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     (FILE 'HOME' ENTERED AT 15:29:51 ON 01 MAY 2003)

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L1             1 S  2002:575765/AN
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L3             STR
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L13            0 S L11 AND L12

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     FILE 'CAPLUS' ENTERED AT 15:41:15 ON 01 MAY 2003
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← applicant's priority doc citation

← 137 cpds in the L1 citation

STR search

← 56 cpds

← these cpds appear only

← remaining cpds

← applicant's priority doc citation

← 33 cites for L10 cpds

93475

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: T. A. Solola Examiner #: 74583 Date: 4/24/03
Art Unit: 1621 Phone Number 305-4490 Serial Number: 10/071,667
Mail Box and Bldg/Room Location: 3E12 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Thanks.

Point of Contact:
Susan Hanley
Technical Info. Specialist
CM1 6B05 Tel: 305-4053

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: _____	NA Sequence (#)	_____	STN:	_____
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Searcher Location: _____	Structure (#)	_____	Questel/Orbit	_____
Date Searcher Picked Up: _____	Bibliographic	_____	Dr.Link	_____
Date Completed: 4/1	Litigation	_____	Lexis/Nexis	_____
Searcher Prep & Review Time: _____	Fulltext	_____	Sequence Systems	_____
Clerical Prep Time: _____	Patent Family	_____	WWW/Internet	_____
Online Time: _____	Other	_____	Other (specify)	_____

PTO-1590 (8-01)

In the Claims

Please amend claims 1, 17, 18, 36-47, 49-51, and 53-55 so that they read as shown below. Please cancel Claims 33 and 34, without prejudice. A copy of the amended claims that shows the changes that were made in this response is attached. The remaining claims are unchanged in this response. The status of the claims is as follows:

- Claims 1-32 and 35-56 are pending.
- Claims 33 and 34 have been cancelled.
- New Claim 56 is submitted to replace Claim 33, with changes relating to formalities.
- Claims 1, 17, 18, 36-47, 49-51, and 53-55 are amended herein.
- Claims 27, 31, 32, and 35 were amended once previously.

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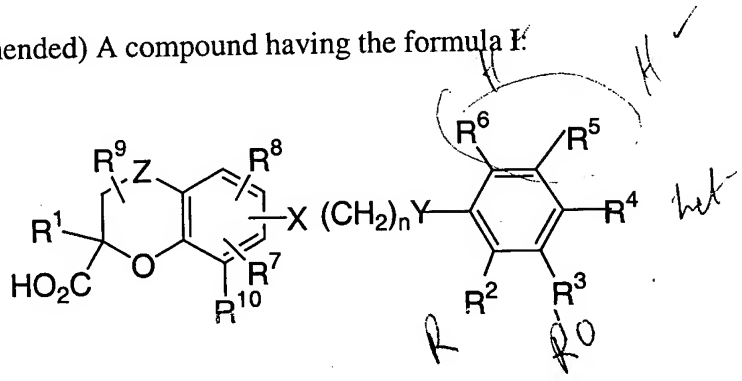
1. (Amended) A compound having the formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Z is selected from the group consisting of CH_2 and C=O;

R^1 is selected from the group consisting of H, -OH, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, -OC_{1-3}alkyl, -OC_{2-3}alkenyl, -OC_{2-3}alkynyl, F, Br, Cl, and Ar, wherein alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl and -Oalkynyl are linear or branched and are optionally substituted with (a) 1-7 halogen

atoms, (b) 1-3 groups independently selected from (i) -OC_{1-3}alkyl, which is optionally substituted with 1-5 halogen atoms, and (ii) phenyl, which is optionally substituted with 1-3 groups independently selected from halogen, C_{1-5}alkyl and -OC_{1-3}alkyl, said C_{1-5}alkyl and -OC_{1-3}alkyl being linear or branched and optionally substituted with 1-5 halogens, or (c) a mixture of (a) and (b);

Ar is Aryl, wherein Aryl is in each instance optionally substituted with 1-5 substituents independently selected from (a) halogen, (b) C_{1-5}alkyl, (c) C_{2-5}alkenyl, (d) C_{2-5}alkynyl, (e) -OC_{1-5}alkyl, (f) –OC_{2-5}alkenyl, (g) –OC_{2-5}alkynyl, (h) -SO_xC_{1-5}alkyl, (i) -$SO_xNR^aR^b$, (j) –SO_xphenyl, (k) –$C(O)C_{1-3}$alkyl, and (l) -$C(O)NR^aR^b$, wherein in each instance, each alkyl, alkenyl and alkynyl is linear or branched and is optionally substituted with (a) 1-5 halogen atoms, (b) 1-2 groups independently selected from -OC_{1-3}alkyl, which is linear or branched and is optionally substituted with 1-5 halogens, or (c) a mixture thereof, and wherein phenyl is optionally substituted with 1-3 substituents independently selected from halogen, C_{1-3}alkyl, and C_{1-3}alkoxy, wherein C_{1-3}alkyl and C_{1-3}alkoxy are linear or branched and are optionally substituted with 1-5 halogens;

x is selected from 0, 1 and 2;

Aryl is a carbocyclic 6-10 membered monocyclic or bicyclic aromatic ring system;

Hetcyc is a 5- or 6-membered saturated or partly saturated monocyclic heterocycle having 1-4 heteroatoms independently selected from N, S, and O in the perimeter of the ring, wherein N may optionally be NR^a and S may optionally be SO or SO_2;

Benzoheterocycle comprises a 5 or 6-membered heterocyclic ring which may be saturated, partly unsaturated or aromatic, and a benzene ring, wherein said heterocyclic ring and said benzene ring are fused together, wherein said heterocyclic ring comprises 1-3 heteroatoms independently selected from O, S, and N in the perimeter of the ring, where N may optionally be NR^a, and S may optionally be SO or SO_2;

R^a and R^b are independently selected from the group consisting of H, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, -$C(O)C_{1-5}$alkyl, -$C(O)C_{2-5}$alkenyl, -$C(O)C_{2-5}$alkynyl, SO_xC_{1-5}alkyl, SO_xphenyl, $SOxNR^dR^e$, -$C(O)NR^dR^e$, halogen, and phenyl, wherein in all instances, alkyl, alkenyl, and

alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1-3 groups independently selected from -OCH_3, -OCF_3 and phenyl, or (c) a mixture thereof, wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C_{1-3}alkyl, and C_{1-3}alkoxy, said C_{1-3}alkyl and C_{1-3}alkoxy being linear or branched and optionally substituted with 1-5 halogens;

R^d and R^e are independently selected from H, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, and phenyl, wherein said alkyl, alkenyl, and alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1-3 groups independently selected from -OCH_3, -OCF_3 and phenyl, or (c) a mixture thereof, wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C_{1-3}alkyl, and C_{1-3}alkoxy, said C_{1-3}alkyl and C_{1-3}alkoxy being linear or branched and optionally substituted with 1-5 halogens;

X and Y are independently selected from the group consisting of O, S, SO, SO_2, NR^a and CH_2;

O, S, N No way

B1

n is an integer from 1-6;

R^2, R^3, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently selected from the group consisting of H, halogen, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, -OH, -OC_{1-5}alkyl, -OC_{2-5}alkenyl, -OC_{2-5}alkynyl, -$C(O)C_{1-5}$alkyl, -$C(O)C_{2-5}$alkenyl, -$C(O)C_{2-5}$alkynyl, -$C(O)OC_{1-5}$alkyl, -$C(O)OC_{2-5}$alkenyl, -$C(O)OC_{2-5}$alkynyl, -$OC(O)C_{1-5}$alkyl, -$OC(O)C_{2-5}$alkenyl, -$OC(O)C_{2-5}$alkynyl, Ar, -OAr, -C(O)Ar, -C(O)OAr, -OC(O)Ar, C_{3-8}Cycloalkyl, -OC_{3-8}Cycloalkyl, -SO_xC_{1-5}alkyl, -$SO_xNR^aR^b$, -SO_xAr, and -$C(O)NR^aR^b$, wherein in each instance, each alkyl, alkenyl, and alkynyl is linear or branched and is optionally substituted with (a) 1-5 halogen atoms, (b) 1-2 groups independently selected from -OC_{1-3}alkyl groups which are linear or branched and are optionally substituted with 1-5 halogens, (c) 1 group Ar or C_{3-6}Cycloalkyl, or (d) a mixture of more than one of (a), (b) and (c);

R^4 is selected from the group consisting of Benzoheterocycle, C_{3-8}Cycloalkyl, Hetcyc, -OC_{3-8}Cycloalkyl and R^c, with the proviso that if R^4 is R^c, then either (1) R^1 is not H, and no more than one of R^2, R^6, and R^{10} is alkyl, or (2) R^2 is Cl, Br or F, and R10 is not alkyl;

wherein Benzoheterocycle, C_{3-8}Cycloalkyl, Hetcyc and -OC_{3-8}Cycloalkyl are each optionally substituted with 1-3 groups independently selected from halogen, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, -OC_{1-5}alkyl, -OC_{2-5}alkenyl, -OC_{2-5}alkynyl, C_{3-8}Cycloalkyl, -SO_xC_{1-5}alkyl,

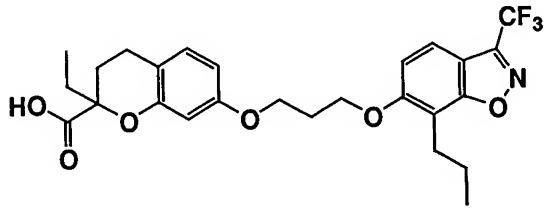
$-SO_xNR^aR^b$,$-SO_x$phenyl, $C(O)C_{1-3}$alkyl and $-C(O)NR^aR^b$, wherein in all instances, said C_{1-5}alkyl, C_{2-5}alkenyl , and C_{2-5}alkynyl groups are linear or branched and are optionally substituted with 1-3 halogens, and wherein Hetcyc, $-OC_{3-8}$Cycloalkyl and C_{3-8}Cycloalkyl may optionally have a C_{3-6}-spiro-cycloalkyl substituent on the ring where gem-disubstitution of a ring carbon is possible, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen;

wherein R^c is selected from the group consisting of halogen, -OH, $-OSO_2C_{1-8}$alkyl, $-OSO_2C_{3-8}$Cycloalkyl, $-OSO_2$Ar, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, $-OC_{1-8}$alkyl, $-OC_{2-8}$alkenyl, $-OC_{2-8}$alkynyl, and Aryl, wherein said $-OSO_2C_{1-8}$alkyl, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, $-OC_{1-8}$alkyl, $-OC_{2-8}$alkenyl, and $-OC_{2-8}$alkynyl are linear or branched, and are optionally substituted with (a) 1-5 halogens, (b) 1-2 groups independently selected from $-OC_{1-3}$alkyl, which are linear or branched and which are optionally substituted with 1-5 halogens, (c) 1 group selected from Aryl and C_{3-8}Cycloalkyl, or (d) a mixture of one or more of (a), (b) and (c), and Aryl and C_{3-8}Cycloalkyl are each optionally substituted as defined under Ar for Aryl and R^4 for C_{3-8}Cycloalkyl;

or alternatively R^4 and the adjacent substituent R^3 or R^5 may be connected to form a 5- or 6-membered heterocyclic ring that may be saturated, partly unsaturated or aromatic fused to the benzene ring, wherein the 5- or 6-membered fused ring comprises 1-3 heteroatoms independently selected from O, S, and N, where N may optionally be NR^a and S may optionally be SO or SO_2, said fused ring optionally also comprising 1-2 C=O groups in the perimeter of the ring, wherein said 5- or 6-membered heterocyclic fused ring is optionally substituted with 1-2 groups independently selected from R^3.

17. (Amended) A compound as recited in Claim 1, wherein R^4 is R^c, R^1 is selected from the group consisting of -OH, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, $-OC_{1-3}$alkyl, $-OC_{2-3}$alkenyl, $-OC_{2-3}$alkynyl, F, Br, Cl, and Ar, wherein alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl and -Oalkynyl are linear or branched and are optionally substituted with (a) 1-7 halogen atoms, (b) 1-3 groups independently selected from (i) $-OC_{1-3}$alkyl, which is optionally substituted with 1-5 halogen atoms, and (ii) phenyl, which is optionally substituted with 1-3 groups independently selected from halogen, C_{1-5}alkyl and $-OC_{1-3}$alkyl, said C_{1-5}alkyl and $-OC_{1-3}$alkyl being linear or branched and optionally

56. (New) A compound represented by a structure shown below, or a pharmaceutically acceptable salt or prodrug thereof, wherein the structure is selected from the group consisting of:



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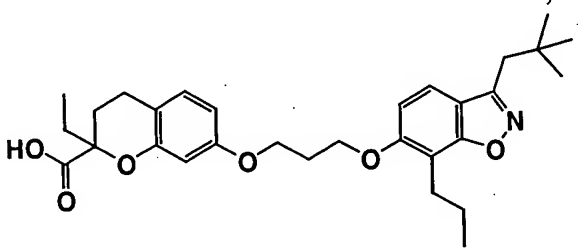

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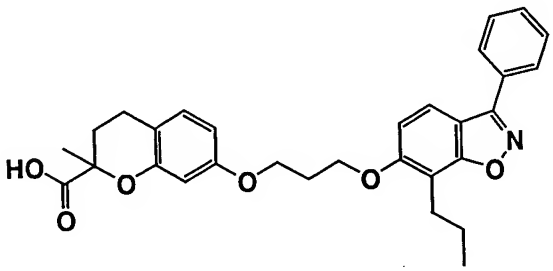

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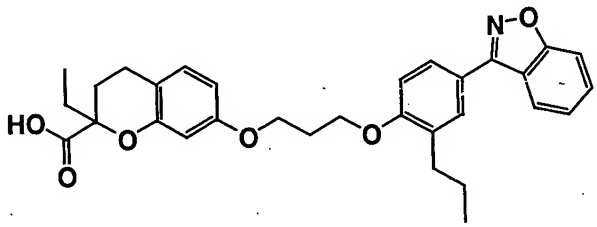

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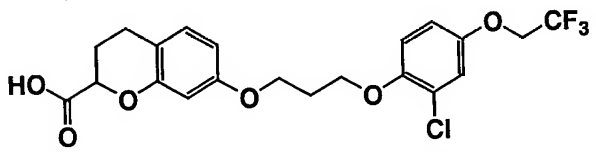

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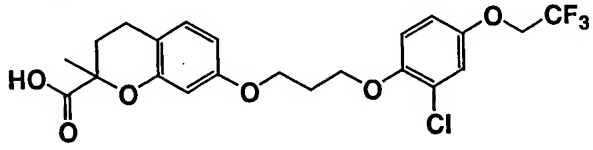

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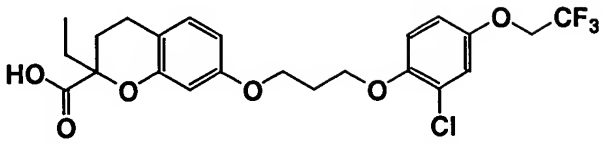
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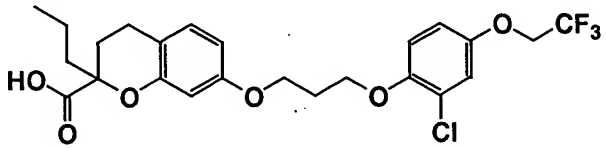
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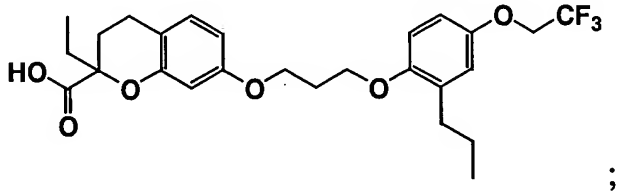
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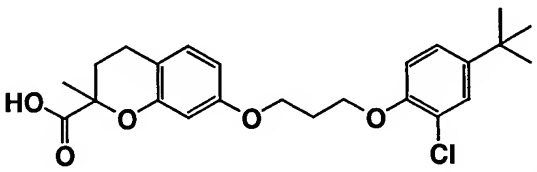
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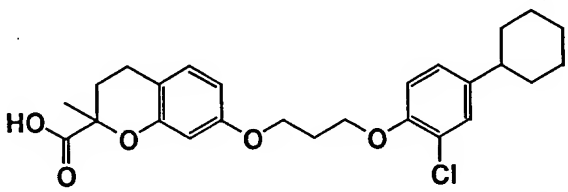
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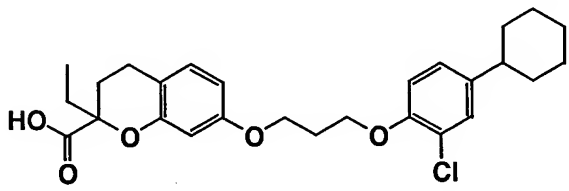
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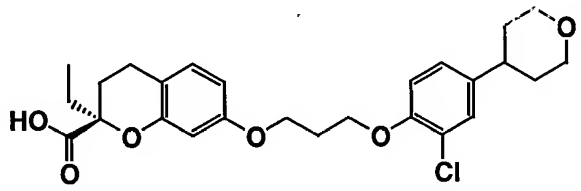
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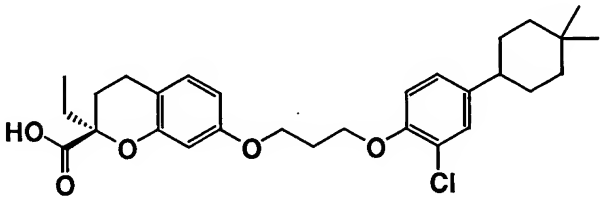
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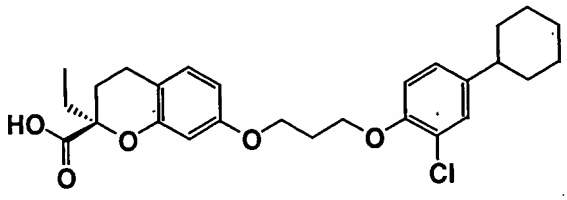
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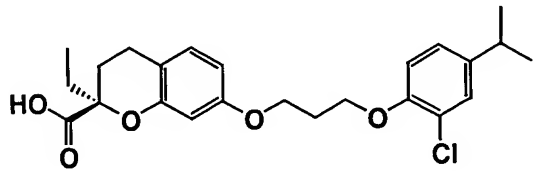
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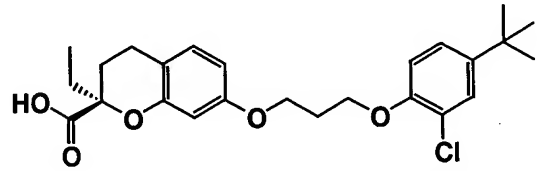
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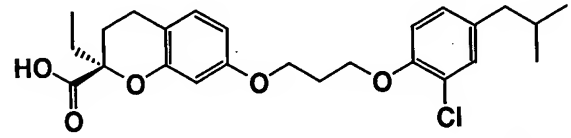
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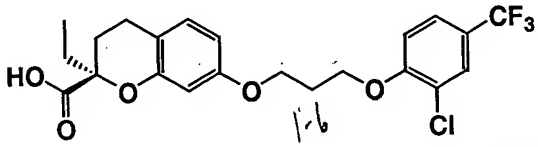
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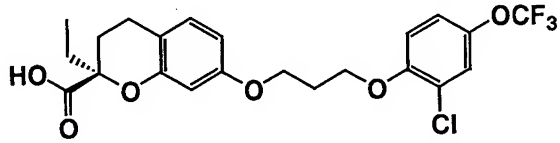
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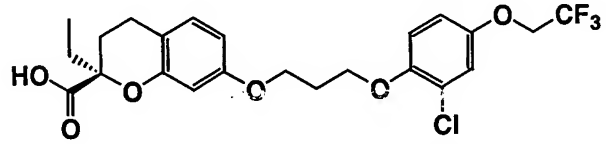
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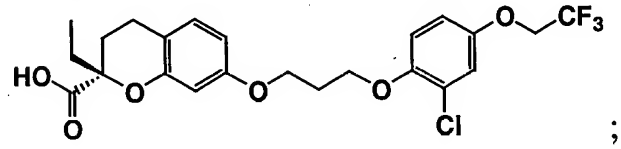
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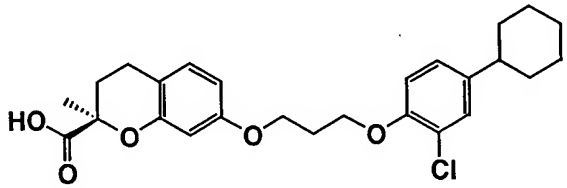
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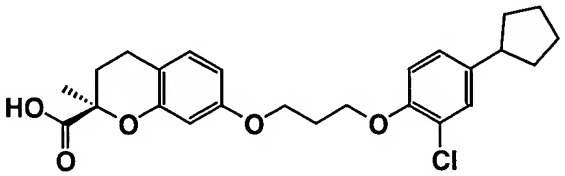
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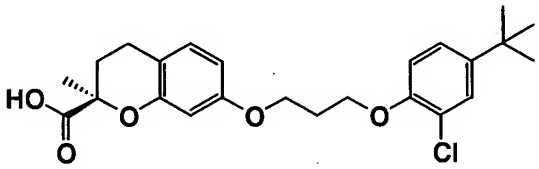
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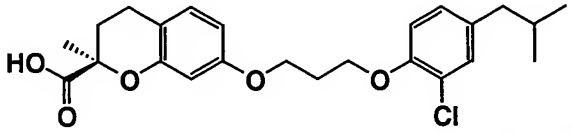
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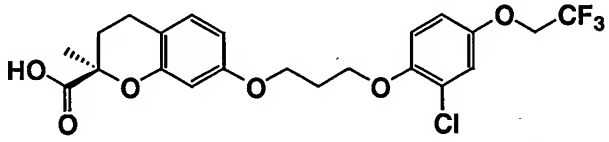
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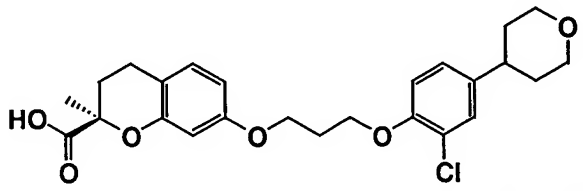
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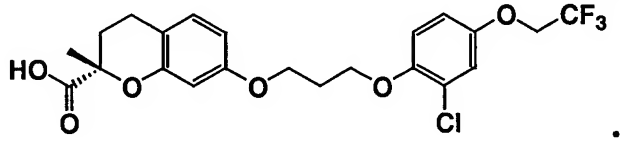
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This packet is a display of compounds that appear only in applicants' priority doc citation

SOLOLA 10/021,667 TO save $, I printed the cpds as ibib abs hitstr

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L3              STR
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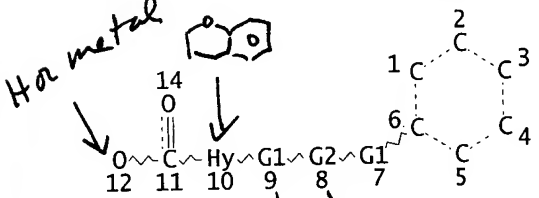
all the cpds that are indexed w/ applicants priority doc citation

parent STR

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CONNECT IS E1  RC AT  12
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E9 C  E1 O  AT  10

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  13

STEREO ATTRIBUTES: NONE
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L6              STR
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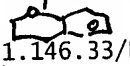
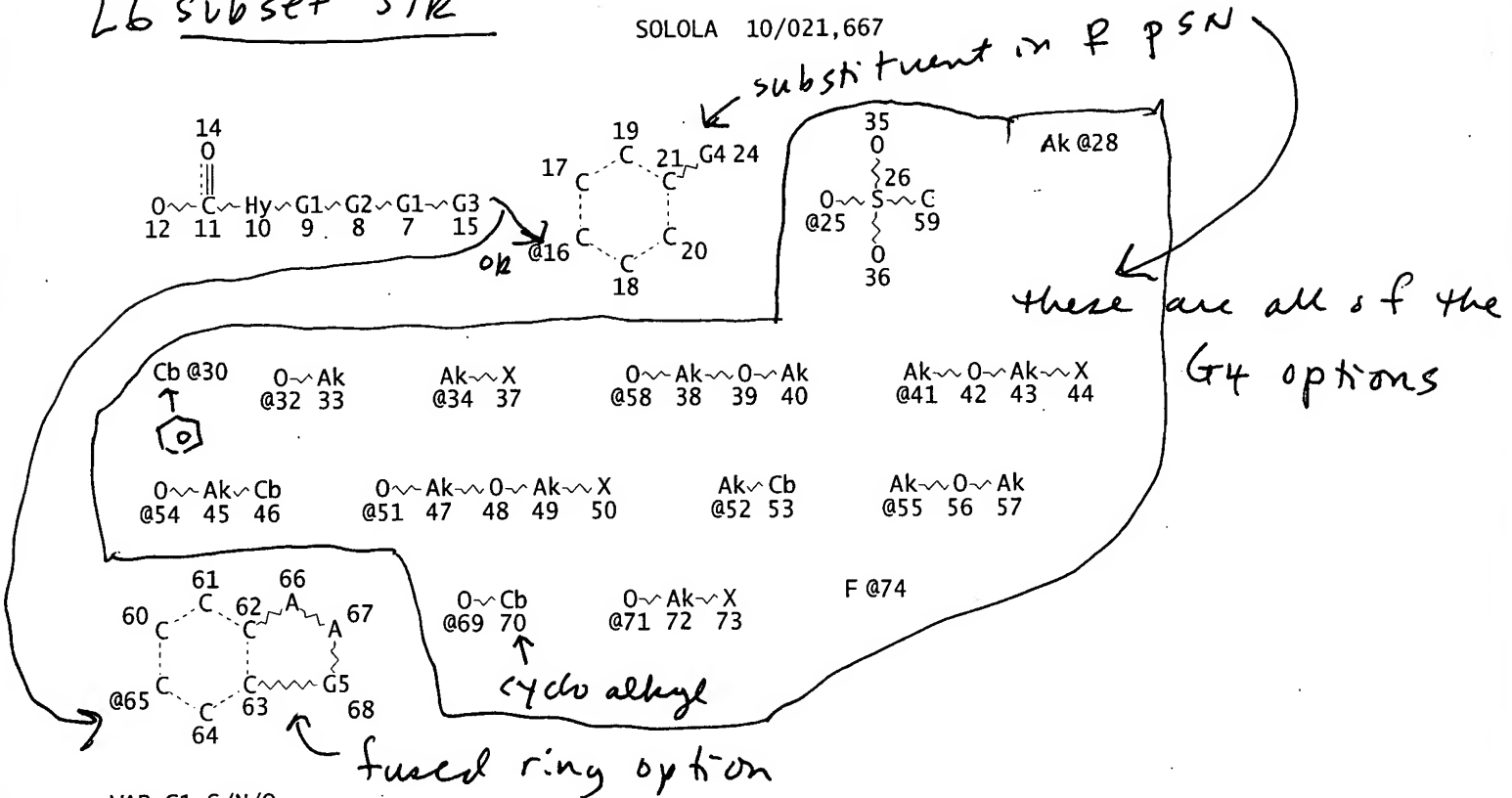
cpd must have  and 

no polymers

160 cpds from parent STR search

L6 subset STR

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REP G5=(1-2) A
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CONNECT IS E1  RC AT  12
CONNECT IS E1  RC AT  28
CONNECT IS E1  RC AT  33
CONNECT IS E1  RC AT  40
CONNECT IS E1  RC AT  57
DEFAULT MLEVEL IS ATOM
GGCAT   IS UNS  AT  30
GGCAT   IS SAT  AT  70
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E9 C  E1 O  AT  10

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NUMBER OF NODES IS  62

STEREO ATTRIBUTES: NONE
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L11           1 SEA FILE=CAPLUS ABB=ON  PLU=ON  L9
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56 cpds

cpds from applicant priority doc cite

29 of the 56 cpds are found only in applicants' priority doc

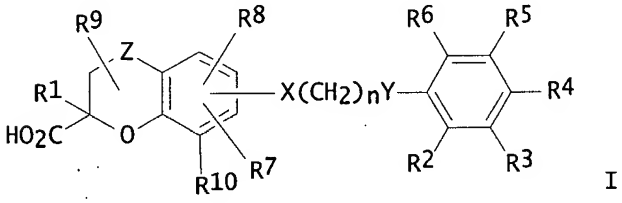
=> d ibib abs hitstr l11

L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:575765 CAPLUS
DOCUMENT NUMBER: 137:140435
TITLE: Benzopyrancarboxylic acid derivatives with PPAR agonist activity for the treatment of diabetes and lipid disorders, and their preparation, pharmaceutical compositions, and use
INVENTOR(S): Sahoo, Soumya P.; Koyama, Hiroo; Miller, Daniel J.; Boueres, Julia K.; Desai, Ranjit C.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 42 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002103242	A1	20020801	US 2001-21667	20011029
WO 2002060434	A2	20020808	WO 2001-US49501	20011026

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-244698P P 20001031
OTHER SOURCE(S): MARPAT 137:140435
GI



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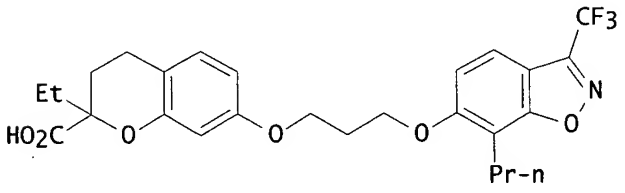


II

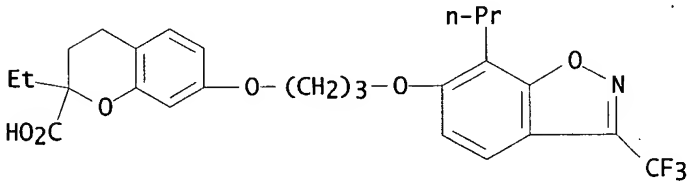
AB A class of benzopyrancarboxylic acid derivs. is disclosed, which comprises compds. that are potent agonists (no data) of peroxisome proliferator

activated receptors (PPAR) alpha and/or gamma, and are therefore useful in the treatment, control, or prevention of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis, inflammation, and other PPAR alpha and/or gamma mediated diseases, disorders and conditions. In particular, compds. I and their pharmaceutically acceptable salts and/or prodrugs are disclosed [wherein: Z = CH2, CO; R1 = H, OH, halo, (un)substituted alk(en/yn)yl, alk(en/yn)yloxy, or aryl; or R1 forms (un)substituted cyclopropane fusion to adjacent C atom; X, Y = O, S, SO, SO2, CH2, (un)substituted NH; n = 1-6; R4 = (un)substituted benzoheterocyclyl, cycloalkyl, heterocyclyl, cycloalkyloxy, halo, OH or derivs., alk(en/yn)yl, alk(en/yn)yloxy, or aryl, etc.; other R groups = H, halo, OH, (un)substituted alk(en/yn)yl, alk(en/yn)yloxy, aryl, aryloxy, aroyl, etc.; or R3R4 or R4R5 = (un)substituted 5- or 6-membered heterocyclic ring]. A list of 29 compds. is claimed, and their prepn. is described. For example, Et 7-hydroxy-4-oxo-4H-chromene-2-carboxylate underwent a sequence of: (1) complete hydrogenation of the enone (98%), (2) etherification of the alc. with PhCH2O(CH2)3Br (66%), (3) alpha ethylation of the ester (70%), (4) hydrogenolytic debenzylation (100%), (5) conversion of the resultant alc. to a bromide (96%), (6) etherification of the bromide with 3-(trifluoromethyl)-7-propyl-6-hydroxybenz[4,5]isoxazole (85%), and (7) alk. hydrolysis (100%), to give title compd. II. PPAR binding assays using human recombinant PPAR are described without data. Co-administration of compds. I with a variety of other drug categories, including a no. of specific drugs, is claimed.

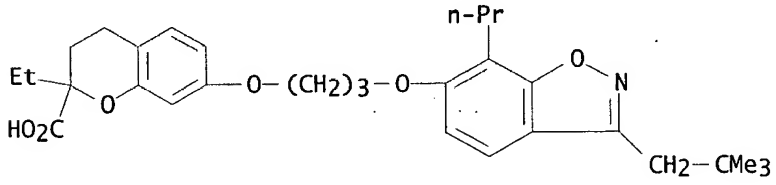
IT **444341-48-4P**, 7-[3-(3-Trifluoromethyl-7-propylbenz[4,5]isoxazol-6-yloxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-49-5P**, 7-[3-[[3-(2,2-Dimethylpropyl)-7-propylbenz[4,5]isoxazol-6-yl]oxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-50-8P**, 7-[3-(3-Phenyl-7-propylbenz[4,5]isoxazol-6-yloxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-51-9P**, 7-[3-[4-(1,2-Benzisoxazol-3-yl)-2-propylphenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-52-0P**, 7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]chromane-2-carboxylic acid **444341-53-1P**, 7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-methylchromane-2-carboxylic acid **444341-54-2P**, 7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-55-3P**, 7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-propylchromane-2-carboxylic acid **444341-56-4P**, 7-[3-[2-Propyl-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-57-5P**, 7-[3-(2-Chloro-4-tert-butylphenoxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-58-6P**, 7-[3-(2-Chloro-4-cyclohexylphenoxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-59-7P**, 7-[3-(2-Chloro-4-cyclohexylphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-60-0P**, (2R)-7-[3-[2-Chloro-4-(4-tetrahydropyranyl)phenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-62-2P**, (2R)-7-[3-[2-Chloro-4-(4,4-dimethylcyclohexyl)phenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-63-3P**, (2R)-7-[3-(2-Chloro-4-cyclohexylphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-64-4P**, (2R)-7-[3-(2-Chloro-4-isopropylphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-65-5P**, (2R)-7-[3-(2-Chloro-4-tert-butylphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-66-6P**, (2R)-7-[3-(2-Chloro-4-isobutylphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-67-7P**, (2R)-7-[3-(2-Chloro-4-trifluoromethylphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid

444341-68-8P, (2R)-7-[3-(2-Chloro-4-trifluoromethoxyphenoxy)propoxy]-2-ethylchromane-2-carboxylic acid **444341-69-9P**, (2R)-7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-70-2P**, (2S)-7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-ethylchromane-2-carboxylic acid **444341-71-3P**, (2R)-7-[3-(2-Chloro-4-cyclohexylphenoxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-72-4P**, (2R)-7-[3-(2-Chloro-4-cyclopentylphenoxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-73-5P**, (2R)-7-[3-(2-Chloro-4-tert-butylphenoxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-74-6P**, (2R)-7-[3-(2-Chloro-4-isobutylphenoxy)propoxy]-2-methylchromane-2-carboxylic acid **444341-75-7P**, (2R)-7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-methylchromane-2-carboxylic acid **444341-76-8P**, (2R)-7-[3-[2-Chloro-4-(4-tetrahydropyranyl)phenoxy]propoxy]-2-methylchromane-2-carboxylic acid **444341-77-9P**, (2S)-7-[3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-methylchromane-2-carboxylic acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of benzopyrancarboxylic acid derivs. as PPAR agonists for treatment of diabetes and lipid disorders)

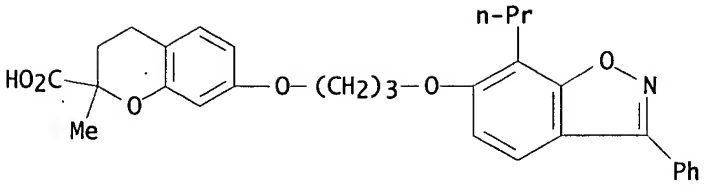
RN 444341-48-4 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 2-ethyl-3,4-dihydro-7-[3-[[7-propyl-3-(trifluoromethyl)-1,2-benzisoxazol-6-yl]oxy]propoxy]- (9CI) (CA INDEX NAME)



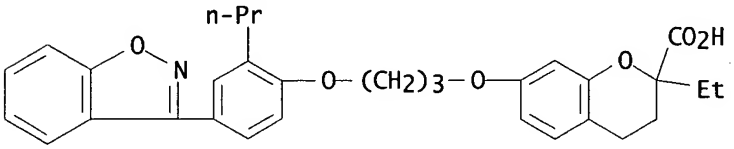
RN 444341-49-5 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[[3-(2,2-dimethylpropyl)-7-propyl-1,2-benzisoxazol-6-yl]oxy]propoxy]-2-ethyl-3,4-dihydro- (9CI) (CA INDEX NAME)



RN 444341-50-8 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-2-methyl-7-[3-[(3-phenyl-7-propyl-1,2-benzisoxazol-6-yl)oxy]propoxy]- (9CI) (CA INDEX NAME)



RN 444341-51-9 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[4-(1,2-benzisoxazol-3-yl)-2-propylphenoxy]propoxy]-2-ethyl-3,4-dihydro- (9CI) (CA INDEX NAME)



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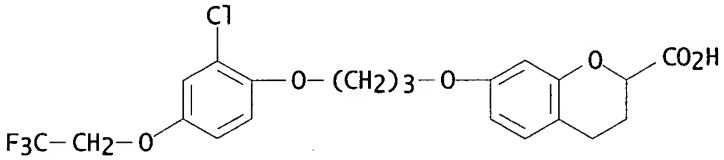
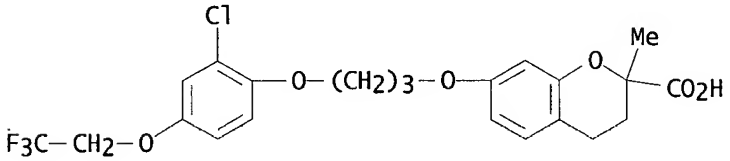


RN 444341-53-1 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-3,4-dihydro-2-methyl- (9CI) (CA INDEX NAME)



RN 444341-54-2 CAPLUS
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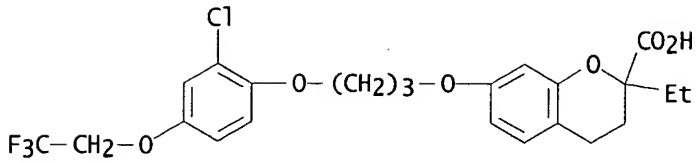

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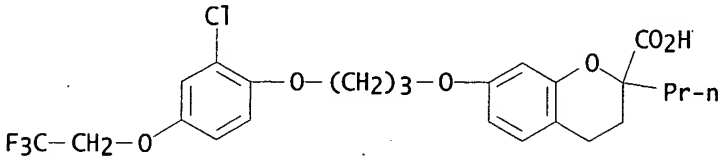
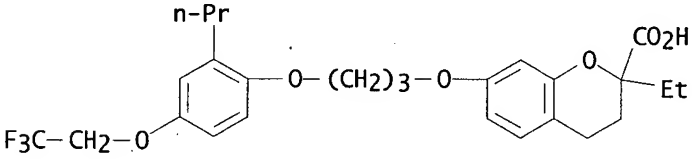
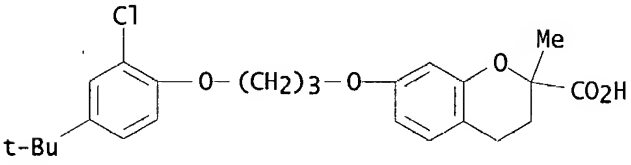


RN 444341-56-4 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 2-ethyl-3,4-dihydro-7-[3-[2-propyl-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]- (9CI) (CA INDEX NAME)



RN 444341-57-5 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(1,1-dimethylethyl)phenoxy]propoxy]-3,4-dihydro-2-methyl- (9CI) (CA INDEX NAME)



RN 444341-58-6 CAPLUS
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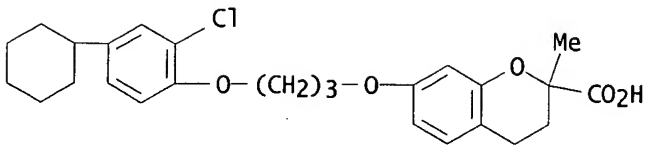

RN 444341-59-7 CAPLUS
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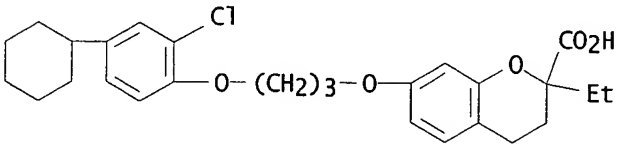
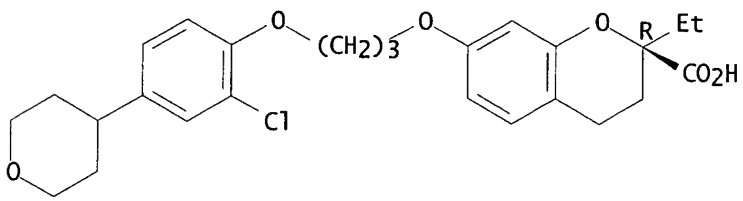


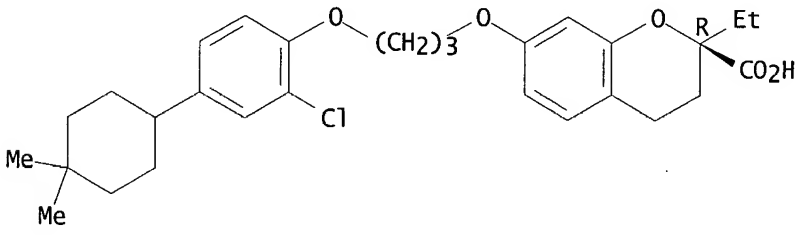
RN 444341-60-0 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(tetrahydro-2H-pyran-4-yl)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



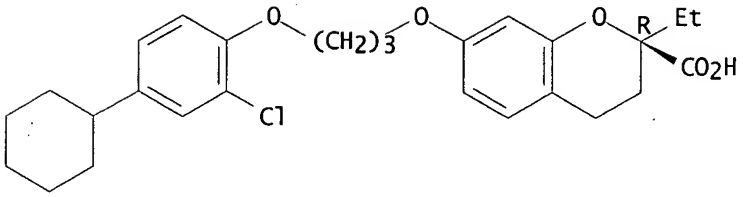
RN 444341-62-2 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(4,4-dimethylcyclohexyl)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



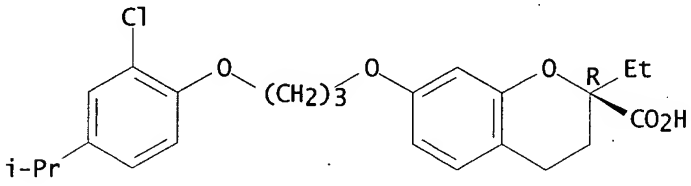
RN 444341-63-3 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-(2-chloro-4-cyclohexylphenoxy)propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



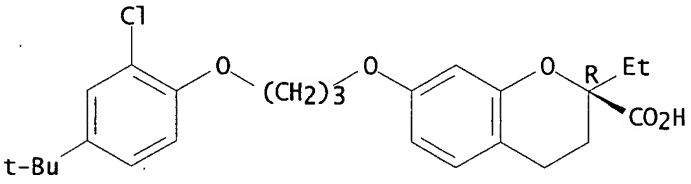
RN 444341-64-4 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(1-methylethyl)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



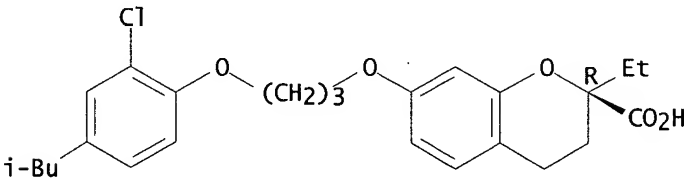
RN 444341-65-5 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(1,1-dimethylethyl)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



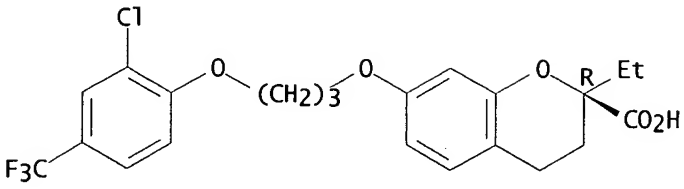
RN 444341-66-6 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2-methylpropyl)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



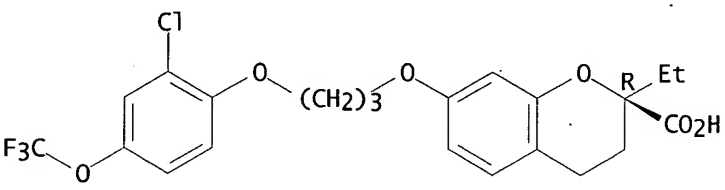
RN 444341-67-7 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(trifluoromethyl)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



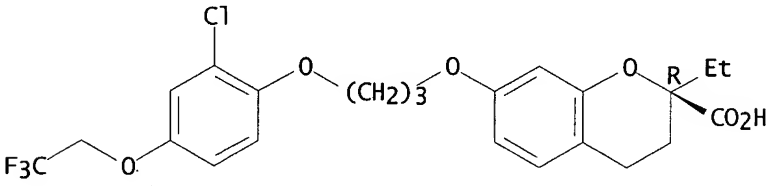
RN 444341-68-8 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(trifluoromethoxy)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



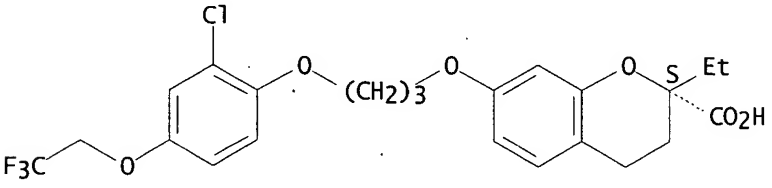
RN 444341-69-9 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444341-70-2 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-2-ethyl-3,4-dihydro-, (2S)- (9CI) (CA INDEX NAME)

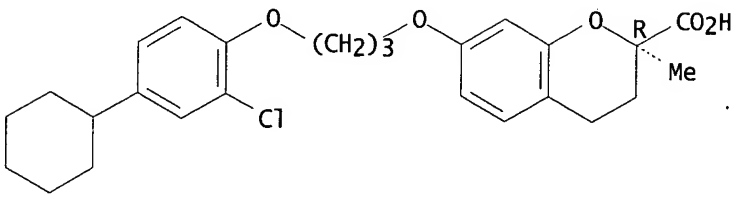
Absolute stereochemistry.



RN 444341-71-3 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-(2-chloro-4-

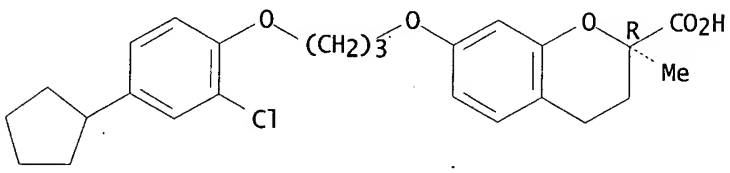
cyclohexylphenoxy)propoxy]-3,4-dihydro-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



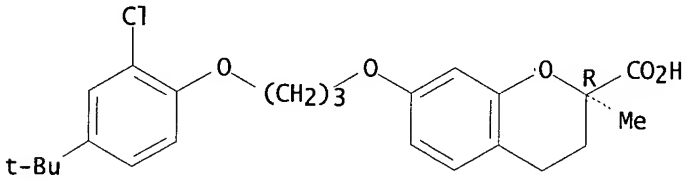
RN 444341-72-4 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-(2-chloro-4-cyclopentylphenoxy)propoxy]-3,4-dihydro-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



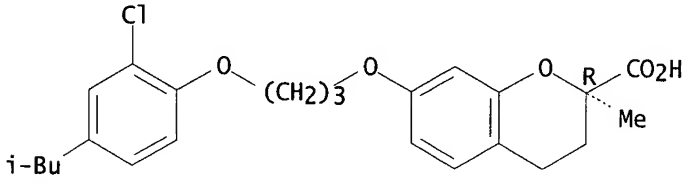
RN 444341-73-5 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(1,1-dimethylethyl)phenoxy]propoxy]-3,4-dihydro-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444341-74-6 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2-methylpropyl)phenoxy]propoxy]-3,4-dihydro-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

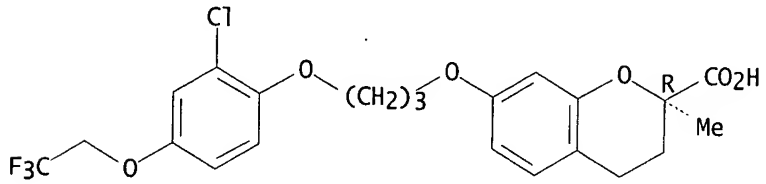
Absolute stereochemistry.



RN 444341-75-7 CAPLUS

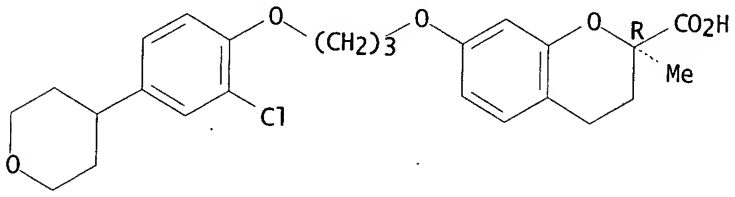
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-3,4-dihydro-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



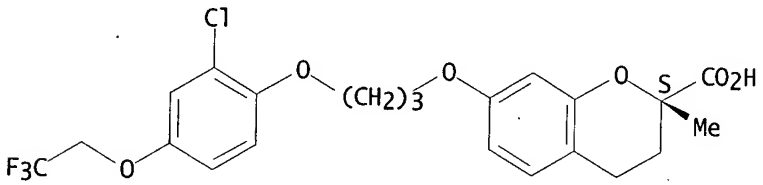
RN 444341-76-8 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(tetrahydro-2H-pyran-4-yl)phenoxy]propoxy]-3,4-dihydro-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 444341-77-9 CAPLUS
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy]-3,4-dihydro-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

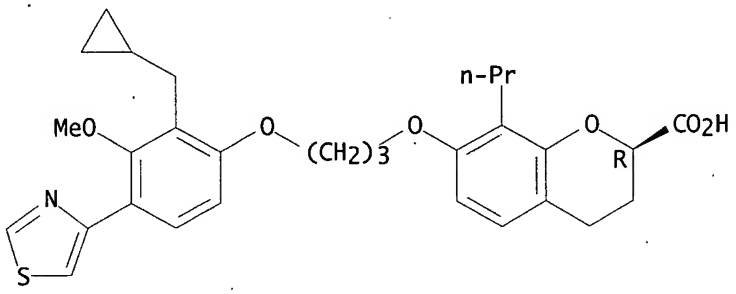


These are the remaing cpds that meet the claimed STR But do NOT appear in applicants priority doc

=> d l10 ide bib abs 1-10

L10 ANSWER 1 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 376346-30-4 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-, (2R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H35 N O6 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

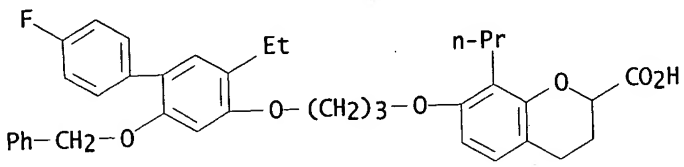
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 136:187 CA
TI Measuring molecular similarity and diversity: total pharmacophore diversity
AU Makara, Gergely M.
CS NeoGenesis Drug Discovery Inc., Cambridge, MA, 02139, USA
SO Journal of Medicinal Chemistry (2001), 44(22), 3563-3571
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB A novel method, total pharmacophore diversity (ToPD), based on known pharmacophore features for numerically defining mol. similarity or diversity is described. The method captures the 3D shape and functionality of mols. by the anal. of relevant intramol. distances to generate a short and descriptive pharmacophoric fingerprint for each mol. The ToPD fingerprints can then be used in diversity anal., clustering, or database searching. Conformational sampling is carried out when needed by the means of mol. dynamics. Our results show that ToPD outperforms a traditional 2D fingerprint technique in all test cases.
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 206268-03-3 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[[5-ethyl-4'-fluoro-2-(phenylmethoxy)[1,1'-biphenyl]-4-yl]oxy]propoxy]-3,4-dihydro-8-propyl-

(9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C37 H39 F O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 137:87495 CA
TI Radiopharmaceuticals for imaging infection and inflammation
IN Barrett, John A.; Cheesman, Edward H.; Harris, Thomas D.; Liu, Shuang; Rajopadhye, Milind; Sworin, Michael
PA Bristol-Myers Squibb Pharma Company, USA
SO U.S., 128 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6416733	B1	20020709	US 1997-943659	19971003
	US 2003007927	A1	20030109	US 2002-109374	20020327
PRAI	US 1996-27955P		19961007		
	US 1997-943659		19971003		

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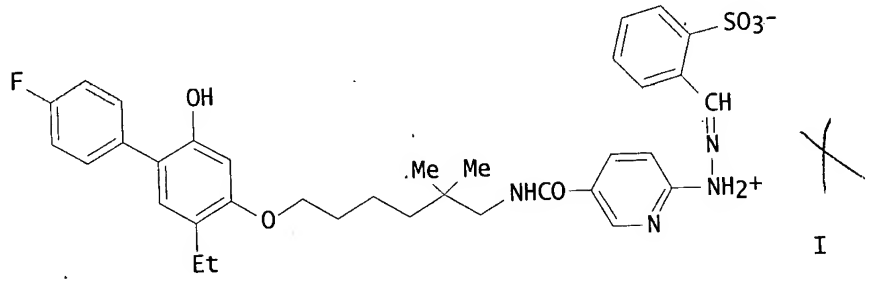


I

AB The present invention provides novel radiopharmaceuticals useful for the diagnosis of infection and inflammation, reagents and kits useful for prepg. the radiopharmaceuticals, methods of imaging sites of infection and/or inflammation in a patient, and methods of diagnosing diseases assocd. with infection or inflammation in patients in need of such

diagnosis. The radiopharmaceuticals bind in vivo to the leukotriene B4 (LTB4) receptor on the surface of leukocytes which accumulate at the site of infection and inflammation. The reagents provided by this invention are also useful for the treatment of diseases assocd. with infection and inflammation. Thus, the leukotriene antagonist (I) was prepd. and shown to be active in an LTB4 human neutrophil (PMN) binding assay. Compd. I was used to prep. 99mTc(tricine)(TPPTS)(4-ethyl-2-(4-fluorophenyl)-[5-[5,5-dimethyl-6-[[[6-diazenido-3-pyridinyl]carbonyl]amino]hexyl]oxy]phenol) (TPPTS = tri(3-sulfonatophenyl)phosphine, sodium salt) which was used to detect inflammation/infection in guinea pig and rabbit focal infection models.

RE.CNT 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 2

AN 136:362949 CA
TI Technetium-99m and indium-111 complexes for simultaneous dual isotope imaging of perfusion and inflammation
IN Carpenter, Alan P., Jr.
PA Bristol-Myers Squibb Pharma Company, USA
SO PCT Int. Appl., 439 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002036173	A2	20020510	WO 2001-US46153	20011102
	WO 2002036173	A3	20020926		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002030576	A5	20020515	AU 2002-30576	20011102
	US 2003003049	A1	20030102	US 2001-2359	20011102
PRAI	US 2000-245554P		20001103		
	WO 2001-US46153		20011102		

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

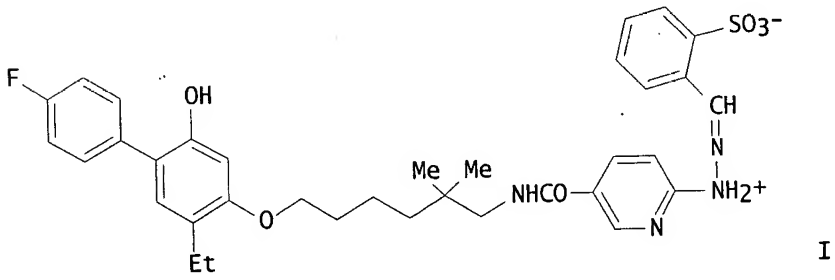
AB The present invention provides novel diagnostic compns., e.g., 99mTc complex of I or 111In complex of II, comprising a radiolabeled LTB4 binding agent and a radiolabeled perfusion imaging agent, wherein the radiolabeled agents have spectrally separable energies, diagnostic kits comprising such compns., and methods of concurrent imaging in a mammal comprising administering a radiolabeled LTB4 binding agent and a radiolabeled perfusion imaging agent, and concurrently detecting the radiolabeled LTB4 binding agent bound at the LTB4 receptor and the radiolabeled perfusion imaging agent. The method is for use in concurrent imaging sites of inflammation and organ perfusion.

REFERENCE 3

AN 128:303347 CA
TI Radiopharmaceuticals for imaging infection and inflammation
IN Barrett, John Andrew; Cheesman, Edward Hollister; Harris, Thomas David; Rajopadhye, Milind
PA Du Pont Merck Pharmaceutical Company, USA
SO PCT Int. Appl., 352 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9815295	A2	19980416	WO 1997-US18096	19971006
	WO 9815295	A3	19980827		
	W: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9852381	A1	19980505	AU 1998-52381	19971006
	AU 736481	B2	20010726		
	BR 9712281	A	19990831	BR 1997-12281	19971006
	CN 1239895	A	19991229	CN 1997-180342	19971006
	EP 999856	A2	20000517	EP 1997-947259	19971006
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	NZ 335539	A	20010629	NZ 1997-335539	19971006
	JP 2001525796	T2	20011211	JP 1998-517680	19971006
	EP 1293214	A2	20030319	EP 2002-79932	19971006
	EP 1293214	A3	20030326		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	ZA 9708956	A	19990416	ZA 1997-8956	19971007
	KR 2000048922	A	20000725	KR 1999-702953	19990406
PRAI	US 1996-726507	19961007			
	EP 1997-947259	19971006			
	WO 1997-US18096	19971006			

GI



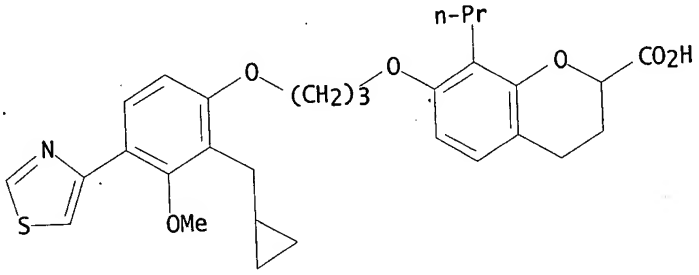
I

AB The present invention provides novel radiopharmaceuticals useful for the diagnosis of infection and inflammation, reagents and kits useful for prepg. the radiopharmaceuticals, methods of imaging sites of infection

and/or inflammation in a patient, and methods of diagnosing diseases assocd. with infection or inflammation in patients in need of such diagnosis. The radiopharmaceuticals bind in vivo to the leukotriene B4 (LTB4) receptor on the surface of leukocytes which accumulate at the site of infection and inflammation. The reagents provided by this invention are also useful for the treatment of diseases assocd. with infection and inflammation. Thus, the leukotriene antagonist (I) was prepd. and shown to be active in an LTB4 human neutrophil (PMN) binding assay. Compd. I was used to prep. 99mTc(tricine)(TPPTS)(4-ethyl-2-(4-fluorophenyl)-[5-[5,5-dimethyl-6-[[[6-diazenido-3-pyridinyl]carbonyl]amino]hexyl]oxy]phenol) (TPPTS = tri(3-sulfonatophenyl)phosphine, sodium salt) which was was used to detect inflammation/infection in guinea pig and rabbit focal infection models.

L10 ANSWER 3 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 162153-47-1 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-, (-)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SC 52799
FS STEREOSEARCH
MF C30 H35 N O6 S
SR CA
LC STN Files: CA, CAPLUS

Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

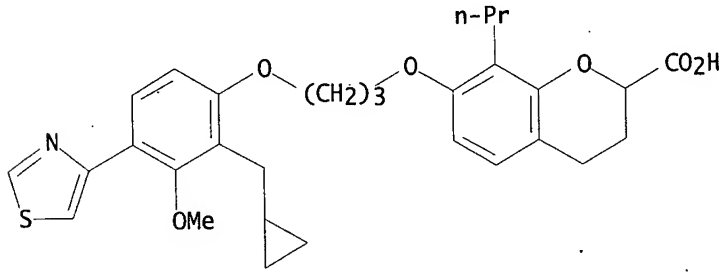
REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68 102(5)
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal

LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

L10 ANSWER 4 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 162153-46-0 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-, (+)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SC 52798
FS STEREOSEARCH
MF C30 H35 N O6 S
SR CA
LC STN Files: CA, CAPLUS, DRUGNL, DRUGUPDATES, USPATFULL

Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 127:239120 CA
TI Compositions comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection
IN Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PA G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SO PCT Int. Appl., 63 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

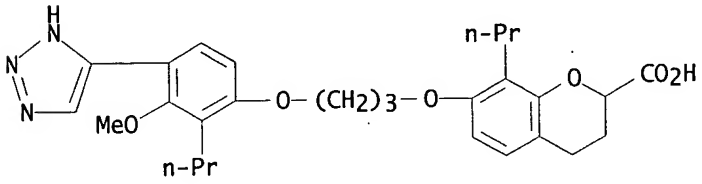
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729775	A1	19970821	WO 1997-US1422	19970211
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2246356	AA	19970821	CA 1997-2246356	19970211
	AU 9722500	A1	19970902	AU 1997-22500	19970211
	EP 880362	A1	19981202	EP 1997-905663	19970211
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2000505445	T2	20000509	JP 1997-529359	19970211
	US 6172096	B1	20010109	US 1998-75633	19980511
PRAI	US 1996-600580	19960213			
	WO 1997-US1422	19970211			

AB Treatment with a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist is described as being useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune diseases.

REFERENCE 2

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

L10 ANSWER 5 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 162105-83-1 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-2-propyl-4-(1H-1,2,3-triazol-4-yl)phenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H35 N3 O6
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

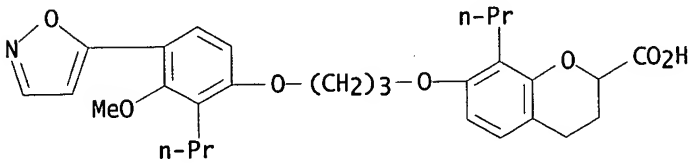
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

L10 ANSWER 6 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 162105-82-0 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[4-(5-isoxazolyl)-3-

methoxy-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C29 H35 N O7
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

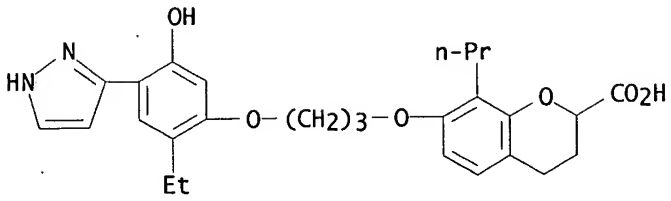
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

L10 ANSWER 7 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 156005-27-5 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-ethyl-5-hydroxy-4-(1H-pyrazol-3-yl)phenoxy]propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H32 N2 O6

SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 132:246369 CA
TI Use of non-peptidyl compounds for the treatment of insulin-related ailments
IN Helmerhorst, Erik; Plewright, Brian Scott
PA Curtin University of Technology, Australia
SO PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000016798	A1	20000330	WO 1999-AU786	19990917
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2345155	AA	20000330	CA 1999-2345155	19990917
	AU 9960707	A1	20000410	AU 1999-60707	19990917
	EP 1115422	A1	20010718	EP 1999-947113	19990917
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	AU 1998-6091		19980922		
	WO 1999-AU786		19990917		

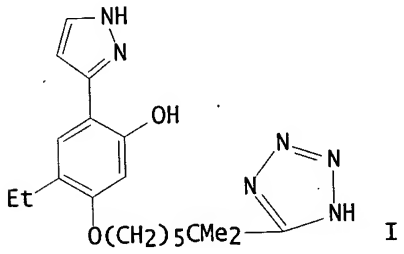
AB The present invention relates to the use of at least a non-peptidyl compd. as a biol. modulator of insulin activity or insulin-related activity for the treatment of insulin-related diseases. Non-peptidyl compds. of the present invention exert their effects by mimicking amino acids spatially located on insulin, enabling those compds. to bind to the insulin receptor or insulin-like receptor causing biol. modulation of the activity of the receptor. A method for identifying a non-peptidyl compd. comprises the steps of: (1) comparing the 3D structure of the non-peptidyl compd. with a 3D pharmacophore of an active site of insulin, and (2) selecting a non-peptidyl compd. The compds. may act either as agonists or antagonists

of insulin or insulin-like activity. Pharmaceutical compns. contg. chem. compds. capable of modulating the biol. activity of insulin are also claimed. For example, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (IM 025) was an antagonist of insulin action. IM 025 caused a dose-dependent decrease in the incorporation of 32P into FYF peptide in insulin-stimulated tubes and inhibited glucose transport in 3T3L1 cells, with IC50 of 150 and 170 .mu.M, resp. 2,4-Dichloro-6-[N-(trifluoromethanesulfonyl)sulfamoylphenyl-3,5-dichloro-2-hydroxybenzene] sulfonate (IM 103) was an agonist of insulin action displaying a biphasic biol. dose response curve with an apex at concn. of 110 .mu.M and an apparent EC50 of 45 .+-. 7 .mu.M.

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 2

AN 121:57380 CA
TI Leukotriene B4 (LTB4) Receptor Antagonists: A Series of (Hydroxyphenyl)pyrazoles
AU Harper, Richard W.; Jackson, William T.; Froelich, Larry L.; Boyd, Robert J.; Aldridge, Timothy E.; Herron, David K.
CS Lilly Research Laboratories, Eli Lilly Company, Indianapolis, IN, 46285, USA
SO Journal of Medicinal Chemistry (1994), 37(15), 2411-20
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI

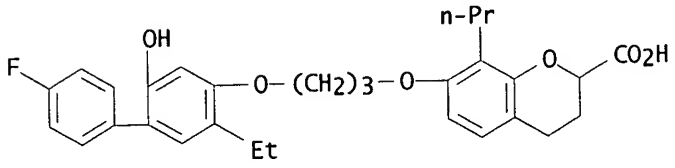


I

AB A series of (hydroxyphenyl)pyrazoles was designed by mol. modeling comparison with the LTB4 structure and prepd. for evaluation as LTB4 receptor antagonists, culminating in the pyrazolylphenol I. Using an assay for inhibition of specific [3H]LTB4 binding to human PMN, it was found that the pyrazole ring could be methylated at N(1) with little loss of activity while methylation at N(2) reduced activity significantly. The structure-activity relationship of the terminal acid group was investigated. Good activity was found with o- and m-phenylalkanoic acids, chromancarboxylic acid, and tetrazole groups. The best in vitro activity was realized with the pyrazole nitrogen unsubstituted and with a six-carbon chain linking the Ph ether oxygen to the tetrazole group. I, having an IC50 of 6.4 .+-. 0.8 nM in the binding assay, was selected for further preclin. evaluation.

L10 ANSWER 8 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 152608-30-5 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)

MF C30 H33 F O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12 REFERENCES IN FILE CA (1957 TO DATE)
11 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 134:366684 CA
TI Preparation of[(phenoxyalkoxy)phenoxy]benzoates and analogs for reversal of multidrug resistance
IN Jedlitschky, Gabriele; Leier, Inka; Keppler, Dietrich
PA Eli Lilly and Company, USA
SO U.S., 28 pp., Cont.-in-part of U.S. 5,543,428.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6235785	B1	20010522	US 1997-793659	19970226
	US 5543428	A	19960806	US 1994-298644	19940831
	DE 4432563	A1	19960314	DE 1994-4432563	19940913
	DE 4432563	C2	19970724		
	WO 9606604	A2	19960307	WO 1995-US11125	19950831
	WO 9606604	A3	19960801		
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	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 2002010213	A1	20020124	US 2001-836429	20010417
	US 2002013370	A1	20020131	US 2001-836567	20010417

PRAI	US 1994-298644	19940831
	DE 1994-4432563	19940913
	WO 1995-US11125	19950831
	US 1997-793659	19970226

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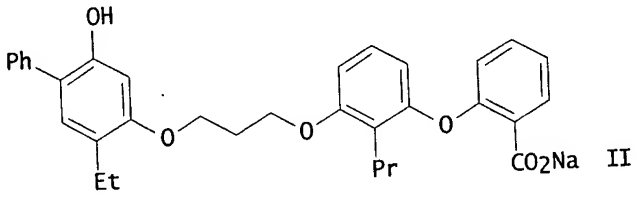

II

AB R1Z1O(CH2)nOZOR [I; R = (un)substituted C6H4CO2H; R1 = (halo)phenyl; Z = 2-(un)substituted 1,3-phenylene; Z1 = 3-alkyl-(un)substituted 1,4-phenylene; n = 3-5] were prepd. Thus, 2,6-(HO)2C6H3Pr was etherified by 2-IC6H4CO2Me and the product etherified by PhZ1O(CH2)3Cl (Z1 = 6-benzyloxy-3-ethyl-1,4-phenylene) to give, in 2 addnl. steps, title compd. II. Data for biol. activity of I were given.

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 2

AN 134:366682 CA
TI Oncolytic combinations for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 270 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034198	A2	20010517	WO 2000-US30941	20001109
	WO 2001034198	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164900P 19991111
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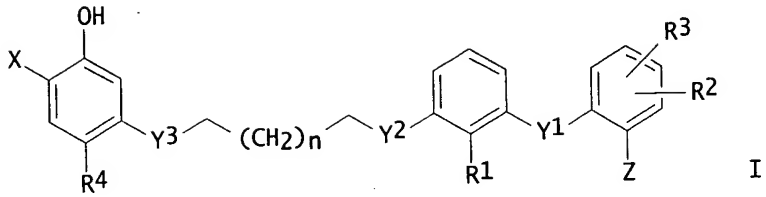

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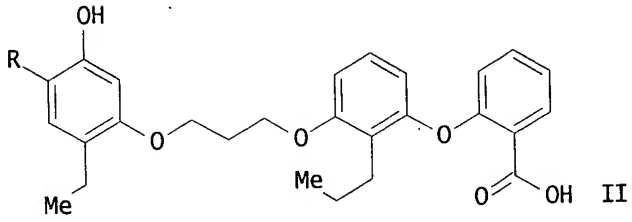

II

AB A method of treating cancer that comprises administering a patient ionizing radiation in conjunction with effective amts. of a 2',2'-difluoronucleoside anti-cancer compd. and a leukotriene LTB4 inhibitor (I) [wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] is disclosed. Examples includes 17 syntheses, 22 formulations, and Lewis lung test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of C57B1 mice with 100 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4), 60 mg/kg of gemcitabine.bul.HCl, and 400 Rads of radiation delayed growth of murine Lewis lung carcinoma by an av. of 32.3 days, compared to a delay of 13.4 days using the gemcitabine.bul.HCl and radiation combination. In addn., the mean no. of lung metastases was reduced from 11.5 to 7.0.

REFERENCE 3

AN 134:366681 CA
TI Oncolytic combinations for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 250 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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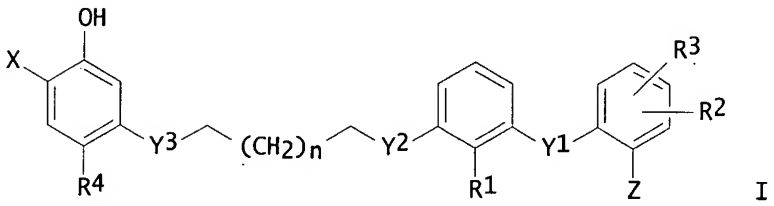
PI WO 2001034197 A2 20010517 WO 2000-US30839 20001109
WO 2001034197 A3 20020510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRAI US 1999-164704P 19991111
GI



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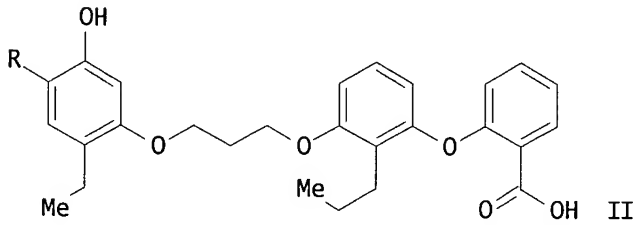

II

AB A method of treating cancer with radiation in conjunction with the administration of a leukotriene LTB4 inhibitor (I) [wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] is disclosed. Examples includes 17 syntheses, 7 formulations, nude mouse xenograft test results, and Lewis lung test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of mice with 100 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4) and 400 Rads of radiation delayed growth of human DU145 prostate carcinoma by an av. of 31.5 days, compared to a delay of 19.2 days using radiation alone. In the Lewis lung test, the mean no. of lung metastases was reduced from 15.5 using radiation alone to 12.0 using the combination

therapy.

REFERENCE 4

AN 134:366680 CA
TI Oncolytic combinations for the treatment of cancer
IN Fleisch, Jerome Herbert; Benjamin, Roger Stuart; Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 283 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034137	A2	20010517	WO 2000-US31039	20001109
	WO 2001034137	A3	20020214		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2000015490	A	20020709	BR 2000-15490	20001109
	EP 1231938	A2	20020821	EP 2000-978535	20001109
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003513916	T2	20030415	JP 2001-536137	20001109
	NO 2002002245	A	20020709	NO 2002-2245	20020510
PRAI	US 1999-164786P		19991111		
	WO 2000-US31039		20001109		

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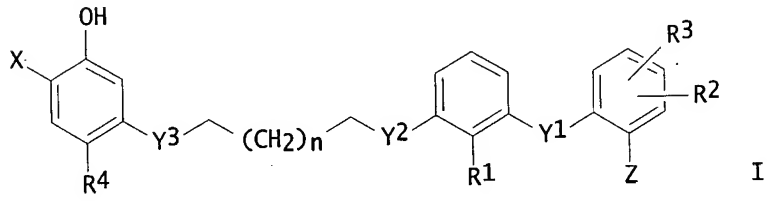

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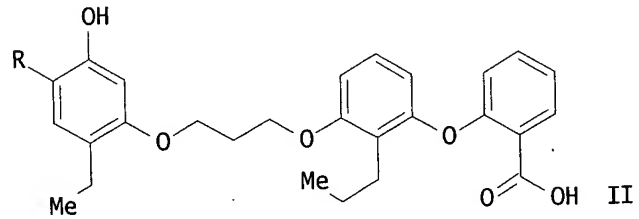

II

AB A method of treating cancer by administration of a 2',2'-difluoronucleoside anti-cancer compd. and a leukotriene LTB4 inhibitor (I)

[wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] is disclosed. Examples includes 17 syntheses, 22 formulations, and mouse xenograft test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of mice with 100 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4) and 60 mg/kg of gemcitabine.bul.HCl delayed growth of LNCaP prostate carcinoma by an av. of 51.2 days, compared to a delay of 12.2 days using the gemcitabine.bul.HCl alone.

REFERENCE 5

AN 134:366679 CA
TI Oncolytic combinations for the treatment of cancer
IN Fleisch, Jerome Herbert; Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034135	A2	20010517	WO 2000-US30944	20001109
	WO 2001034135	A3	20020321		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1231939	A2	20020821	EP 2000-983695	20001109
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003513914	T2	20030415	JP 2001-536135	20001109
PRAI	US 1999-164713P		19991111		
	WO 2000-US30944		20001109		

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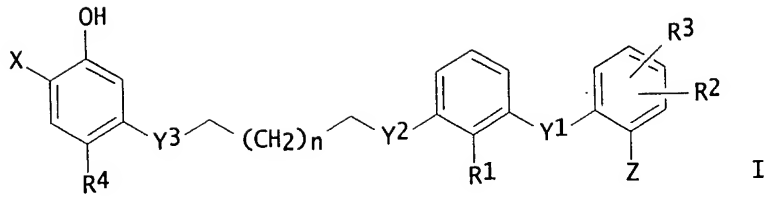

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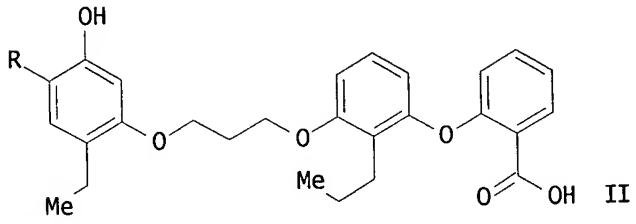

II

AB A method of treating cancer with therapeutic combinations of a leukotriene LTB4 inhibitor (I) [wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] and an anti-cancer agent is disclosed. Examples includes 17 syntheses, 7 formulations, and nude mouse xenograft test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of mice with 200 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4) and 50 mg/kg of carboplatin delayed growth of human H460 non-small cell lung carcinoma by an av. of 33.3 days, compared to a delay of 13.9 days using the leukotriene antagonist alone or 10.7 days using carboplatin alone.

REFERENCE 6

AN 132:246369 CA
TI Use of non-peptidyl compounds for the treatment of insulin-related ailments
IN Helmerhorst, Erik; Plewright, Brian Scott
PA Curtin University of Technology, Australia
SO PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000016798	A1	20000330	WO 1999-AU786	19990917

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,

CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2345155	AA	20000330	CA 1999-2345155	19990917	
AU 9960707	A1	20000410	AU 1999-60707	19990917	
EP 1115422	A1	20010718	EP 1999-947113	19990917	

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRAI AU 1998-6091 19980922
WO 1999-AU786 19990917

AB The present invention relates to the use of at least a non-peptidyl compd. as a biol. modulator of insulin activity or insulin-related activity for the treatment of insulin-related diseases. Non-peptidyl compds. of the present invention exert their effects by mimicking amino acids spatially located on insulin, enabling those compds. to bind to the insulin receptor or insulin-like receptor causing biol. modulation of the activity of the receptor. A method for identifying a non-peptidyl compd. comprises the steps of: (1) comparing the 3D structure of the non-peptidyl compd. with a 3D pharmacophore of an active site of insulin, and (2) selecting a non-peptidyl compd. The compds. may act either as agonists or antagonists of insulin or insulin-like activity. Pharmaceutical compns. contg. chem. compds. capable of modulating the biol. activity of insulin are also claimed. For example, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (IM 025) was an antagonist of insulin action. IM 025 caused a dose-dependent decrease in the incorporation of 32P into FYF peptide in insulin-stimulated tubes and inhibited glucose transport in 3T3L1 cells, with IC50 of 150 and 170 .mu.M, resp. 2,4-Dichloro-6-[N-(trifluoromethanesulfonyl)sulfamoylphenyl-3,5-dichloro-2-hydroxybenzene] sulfonate (IM 103) was an agonist of insulin action displaying a biphasic biol. dose response curve with an apex at concn. of 110 .mu.M and an apparent EC50 of 45 .+-. 7 .mu.M.

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 7

AN 129:144547 CA
TI The discovery of LY293111, a novel, potent and orally active leukotriene B4 receptor antagonist of the biphenylphenol class
AU Sofia, M. J.; Floreancig, P.; Bach, N.; Baker, S. R.; Nelson, K.; Sawyer, J. S.; Baldwin, R.; Cockerham, S. L.; Fleisch, J. H.; Froelich, L. L.; Jackson, W. T.; Marder, P.; Roman, C. R.; Saussy, D. L., Jr.; Silbaugh, S. A.; Spaethe, S. M.; Stengel, P. W.
CS Lilly Research Labs, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Advances in Experimental Medicine and Biology (1997), 400A(Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury 2, Pt. A), 381-386
CODEN: AEMBAP; ISSN: 0065-2598
PB Plenum Publishing Corp.
DT Journal
LA English
AB The authors report on the discovery of LY293111 a novel and potent leukotriene B4 receptor antagonist with exceptional oral activity. The authors discovered LY293111 by studying the effect of the ortho-phenol substituent on receptor binding and functional antagonism of

biphenylphenol related compds. In vivo antagonism of leukotriene B4-induced bronchoconstriction in guinea pig airways was also studied for these related compds., and the effect of acid structure on receptor binding and functional antagonism was reported. LY293111 sodium salt is currently undergoing human clin. evaluation as an anti-inflammatory agent.

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 8

AN 126:74591 CA
TI Preparation of biphenylyloxyalkylarenes as leukotriene antagonists for the treatment or prevention of Alzheimer's disease.
IN Altstiel, Larry Douglas; Fleisch, Jerome Herbert
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 124 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 743064	A1	19961120	EP 1996-303346	19960513
	R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	WO 9636347	A1	19961121	WO 1996-US6773	19960513
	W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM				
	RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9658572	A1	19961129	AU 1996-58572	19960513
PRAI	US 1995-443179	19950517			
	WO 1996-US6773	19960513			

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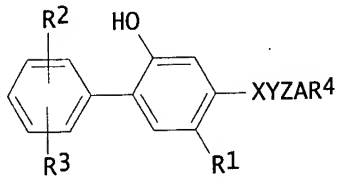

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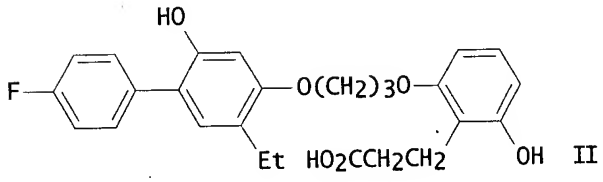


II

AB Use of compds. having leukotriene antagonist activity, e.g., title compds. [I; R1 = alkyl, alkenyl, alkynyl, alkoxy, alkylthio, halo, R2-substituted Ph; R2, R3 = H, halo, OH, alkyl, alkoxy, alkylthio, alkylsulfinyl,

alkylsulfonyl, CF3, dialkylamino; X = O, S, CO, CH2; Y = O, CH2; XY = CH:CH, C.tplbond.C; Z = alkylene; A = bond, O, S, CH:CH, etc.; R4 = (substituted) (hetero)aryl; with provisos] for manuf. of a medicament for treating or preventing Alzheimer's disease is claimed. Thus, 5-hydroxybenzopyran-2-one and 3-(2-ethyl-4-(4-fluorophenyl)-5-benzyloxyphenyl)propyl iodide were stirred with NaH in Me2SO to give 5-[3-(2-ethyl-4-(4-fluorophenyl)-5-benzyloxyphenyl)propoxy]benzopyran-2-one. This was converted to title compd. (II), which displaced [3H]-LTB4 from guinea pig lung membrane prepns. with pKi = 9.01. I drug formulations are given.

REFERENCE 9

AN 125:58323 CA
TI Methods for identifying and treating resistant tumors using [(phenoxyalkoxy)phenoxy]benzoic acids and (phenoxyalkoxy)benzopyrans.
IN Sawyer, Jason Scott; Spaethe, Stephen M.; Starling, James Jacob; Jedlitschky, Gabriele; Leier, Inka; Keppler, Dietrich
PA Lilly, Eli, and Co., USA; Deutsches Krebsforschungszentrum
SO PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9606604	A2	19960307	WO 1995-US11125	19950831
	WO 9606604	A3	19960801		
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5543428	A	19960806	US 1994-298644	19940831
	DE 4432563	A1	19960314	DE 1994-4432563	19940913
	DE 4432563	C2	19970724		
	AU 9535434	A1	19960322	AU 1995-35434	19950831
	EP 777472	A2	19970611	EP 1995-932371	19950831
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
	JP 10505348	T2	19980526	JP 1995-508977	19950831
	US 6235785	B1	20010522	US 1997-793659	19970226
	US 2002010213	A1	20020124	US 2001-836429	20010417
	US 2002013370	A1	20020131	US 2001-836567	20010417

PRAI US 1994-298644 19940831
DE 1994-4432563 19940913
WO 1995-US11125 19950831
US 1997-793659 19970226
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention provides a method of identifying and reversing multidrug resistance in tumors, comprising administration of compds. I [R1 = YC6H4 or Ac; Y = H or halo; R2, R4 = H, OH, or OMe; R3 = C1-6 alkyl; n = 3-5; A = Q1 or Q2; R5 = H, C1-6 alkyl, C2-5 alkenyl or alkynyl, CH2Ph, Ph; R6 =

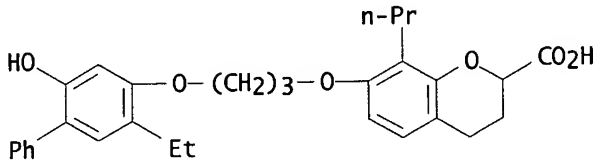
H, halo; R7 = CO2H or 5-tetrazolyl; T = bond, CH2, O, CO, S(O)q; q = 0-2; provided that when one of R2 and R4 = OH or OMe, then the other must = H]. Also provided are test kits and assay methodol. for measurement of MRP protein inhibition. For example, 2-BrC6H4SH was oxidized to the disulfide (43%), which was coupled with lithiated 3-(allyloxy)bromobenzene to give 76% 2-[[3-(allyloxy)phenyl]thio]bromobenzene. This underwent lithiation, carbonation, and esterification to give 68% intermediate II. This underwent Claisen rearrangement to give 41% 2-allyl-3-hydroxy and 27% 4-allyl-3-hydroxy products. The former isomer underwent etherification (66%), hydrogenation (47%), and hydrolysis (100%), to give title compd. III. In a test for reversal of resistance to adriamycin in HL60/ADR cells, III at 20 .mu.M plus adriamycin gave 73% inhibition of cell growth, vs. no effect for adriamycin alone. Results from a variety of bioassays are given, demonstrating that multi-drug resistance can be reversed by blocking the transport function of MRP protein.

REFERENCE 10

AN 124:55467 CA
TI Synthetic and Structure/Activity Studies on Acid-Substituted 2-Arylphenols: Discovery of 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]- propoxy]phenoxy]benzoic Acid, a High-Affinity Leukotriene B4 Receptor Antagonist
AU Sawyer, J. Scott; Bach, Nicholas J.; Baker, S. Richard; Baldwin, Ronald F.; Borromeo, Peter S.; Cockerham, Sandra L.; Fleisch, Jerome H.; Floreancig, Paul; Froelich, Larry L.; et al.
CS Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SO Journal of Medicinal Chemistry (1995), 38(22), 4411-32
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB Structural derivs. of LY255283 have been studied as receptor antagonists of leukotriene B4. Substitution of the 2-hydroxyacetophenone subunit of 1-[5-Ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone (LY255283) with a 2-arylphenol group provided entry into several new series that feature various mono- and diacidic core functionality. These new analogs, the subject of a broad structure-activity investigation, displayed significantly increased in vitro and in vivo activity as receptor antagonists of LTB4. A series of diaryl ether carboxylic acids demonstrated esp. interesting activity and led to the discovery of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid (LY293111), a 2-arylphenol-substituted diaryl ether carboxylic acid which displayed potent binding to human neutrophils (IC50 = 17 .+-. 4.6 nM) and guinea pig lung membranes (IC50 = 6.6 .+-. 0.71 nM), inhibition of LTB4-induced expression of the CD11b/CD18 receptor on human neutrophils (IC50 = 3.3 .+-. 0.81 nM), and inhibition of LTB4-induced contraction of guinea pig lung parenchyma (pKB = 8.7 .+-. 0.16). 801Vivo, LY293111 demonstrated potent activity in inhibiting LTB4-induced airway obstruction in the guinea pig when dosed by the oral (ED50 = 0.40 mg/kg) or i.v. (ED50 = 0.014 mg/kg) routes. A specific LTB4 receptor antagonist, LY293111 had little effect on inhibiting contractions of guinea pig lung parenchyma induced by leukotriene D4 (LTD4), histamine, carbachol, or U46619. LY293111 was chosen as a clih. candidate and is currently in phase I studies for a variety of inflammatory diseases.

L10 ANSWER 9 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 152608-29-2 REGISTRY

CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[(5-ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)
MF C30 H34 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1957 TO DATE)
6 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 134:366682 CA
TI Oncolytic combinations for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 270 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034198	A2	20010517	WO 2000-US30941	20001109
	WO 2001034198	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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PRAI US 1999-164900P 19991111
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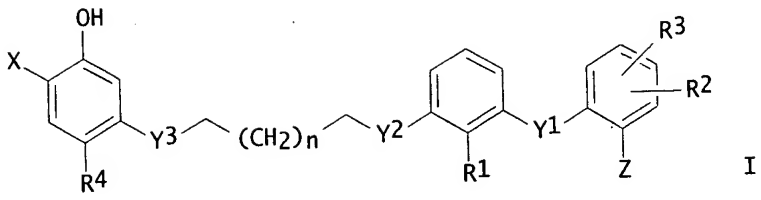

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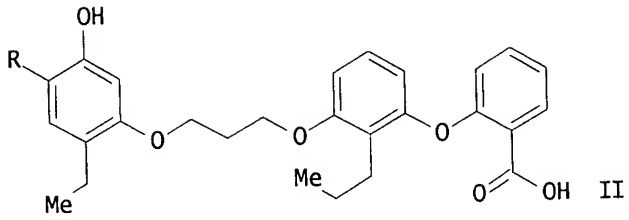

II

AB A method of treating cancer that comprises administering a patient ionizing radiation in conjunction with effective amts. of a 2',2'-difluoronucleoside anti-cancer compd. and a leukotriene LTB4 inhibitor (I) [wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] is disclosed. Examples includes 17 syntheses, 22 formulations, and Lewis lung test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of C57B1 mice with 100 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4), 60 mg/kg of gemcitabine.bul.HCl, and 400 Rads of radiation delayed growth of murine Lewis lung carcinoma by an av. of 32.3 days, compared to a delay of 13.4 days using the gemcitabine.bul.HCl and radiation combination. In addn., the mean no. of lung metastases was reduced from 11.5 to 7.0.

REFERENCE 2

AN 134:366681 CA
TI Oncolytic combinations for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 250 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2001034197 A2 20010517 WO 2000-US30839 20001109
WO 2001034197 A3 20020510
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PRAI US 1999-164704P 19991111
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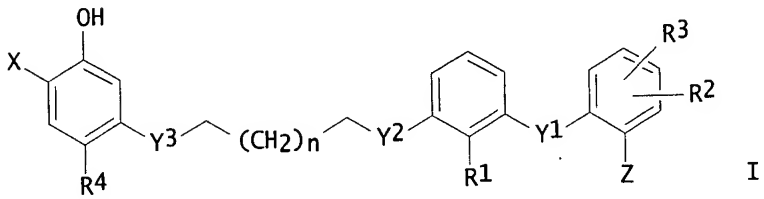

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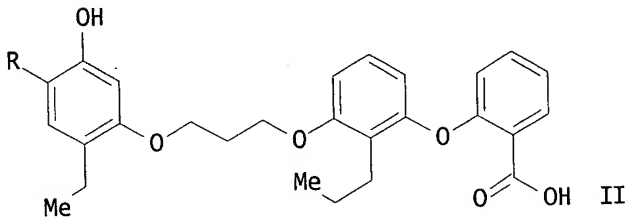

II

AB A method of treating cancer with radiation in conjunction with the administration of a leukotriene LTB4 inhibitor (I) [wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] is disclosed. Examples includes 17 syntheses, 7 formulations, nude mouse xenograft test results, and Lewis lung test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of mice with 100 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4) and 400 Rads of radiation delayed growth of human DU145 prostate carcinoma by an av. of 31.5 days, compared to a delay of 19.2 days using radiation alone. In the Lewis lung test, the mean no. of lung metastases was reduced from 15.5 using radiation alone to 12.0 using the combination

therapy.

REFERENCE 3

AN 134:366680 CA
TI Oncolytic combinations for the treatment of cancer
IN Fleisch, Jerome Herbert; Benjamin, Roger Stuart; Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 283 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	WO 2001034137	A3	20020214		
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	BR 2000015490	A	20020709	BR 2000-15490	20001109
	EP 1231938	A2	20020821	EP 2000-978535	20001109
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003513916	T2	20030415	JP 2001-536137	20001109
	NO 2002002245	A	20020709	NO 2002-2245	20020510
PRAI	US 1999-164786P		19991111		
	WO 2000-US31039		20001109		

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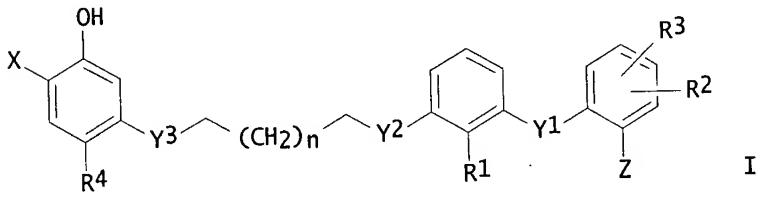

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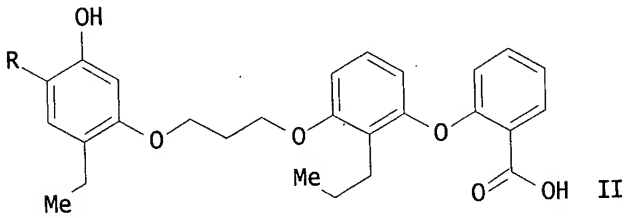

II

AB A method of treating cancer by administration of a 2',2'-difluoronucleoside anti-cancer compd. and a leukotriene LTB4 inhibitor (I)

[wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] is disclosed. Examples includes 17 syntheses, 22 formulations, and mouse xenograft test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of mice with 100 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4) and 60 mg/kg of gemcitabine.bul.HCl delayed growth of LNCaP prostate carcinoma by an av. of 51.2 days, compared to a delay of 12.2 days using the gemcitabine.bul.HCl alone.

REFERENCE 4

AN 134:366679 CA
TI Oncolytic combinations for the treatment of cancer
IN Fleisch, Jerome Herbert; Sawyer, Jason Scott; Teicher, Beverly Ann; Beight, Douglas Wade; Smith, Edward C. R.; McMillen, William Thomas
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034135	A2	20010517	WO 2000-US30944	20001109
	WO 2001034135	A3	20020321		
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	EP 1231939	A2	20020821	EP 2000-983695	20001109
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PRAI	US 1999-164713P		19991111		
	WO 2000-US30944		20001109		

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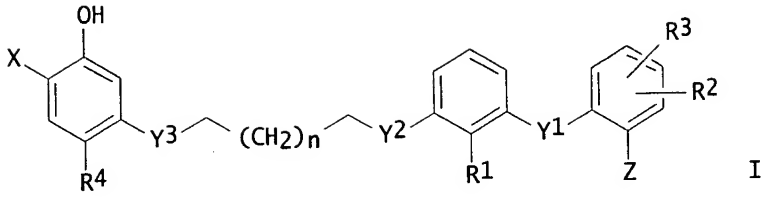

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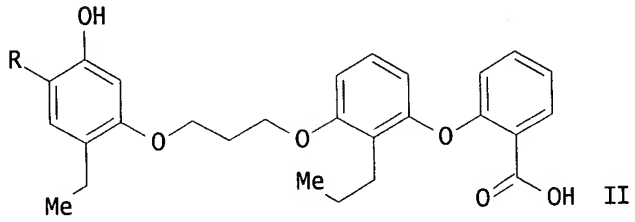

II

AB A method of treating cancer with therapeutic combinations of a leukotriene LTB4 inhibitor (I) [wherein X = a 5-membered (un)substituted heterocycle or fused bicyclic radical consisting of a carbocyclic group fused to 2 adjacent C atoms of a 5-membered (un)substituted heterocycle; Y1 = a bond or divalent linking group contg. 1-9 atoms; Y2 and Y3 = independently CH2, O, or S; Z = an acidic group; R1 = (alk)aryl, cycloalkyl, (ar)alkyl, (ar)alkenyl, alkynyl, haloalkyl, aryloxy, or alkoxy; R2 = H, halo(alkyl), alkoxy, (cyclo)alkyl, acidic group, or (CH2)1-7-acidic group; R3 = (cyclo)alkyl, (CH2)1-7-cycloalkyl, alkenyl, alkynyl, benzyl, or aryl; n = 0-6] and an anti-cancer agent is disclosed. Examples includes 17 syntheses, 7 formulations, and nude mouse xenograft test results. For instance, benzylation of 1-[2-hydroxy-4-(3-chloropropoxy)-5-ethylphenyl]ethanone (69%), coupling the ethanone with 2-(3-hydroxy-2-propylphenoxy)benzoic acid Me ester (72%), oxidn. to give the .alpha.-hydroxy ketone (31%), cyclization with triflic anhydride and formamide to give the oxazole (6%), debenzylation with BF3.bul.OEt2 (45%), and deesterification (92%) afforded II (R = 4-oxazolyl). Treatment of mice with 200 mg/kg of the LTB4 antagonist, 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid (II; R = 4-FC6H4) and 50 mg/kg of carboplatin delayed growth of human H460 non-small cell lung carcinoma by an av. of 33.3 days, compared to a delay of 13.9 days using the leukotriene antagonist alone or 10.7 days using carboplatin alone.

REFERENCE 5

AN 126:74591 CA
TI Preparation of biphenylyloxyalkylarenes as leukotriene antagonists for the treatment or prevention of Alzheimer's disease.
IN Altstiel, Larry Douglas; Fleisch, Jerome Herbert
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 124 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 743064	A1	19961120	EP 1996-303346	19960513

R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE

WO 9636347 A1 19961121 WO 1996-US6773 19960513
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM
RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
AU 9658572 A1 19961129 AU 1996-58572 19960513
PRAI US 1995-443179 19950517
WO 1996-US6773 19960513

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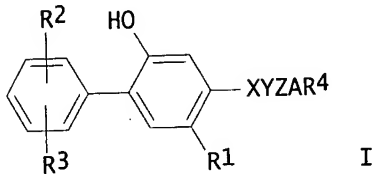

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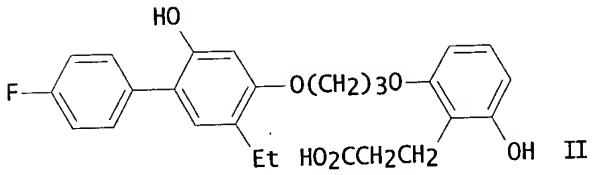

II

AB Use of compds. having leukotriene antagonist activity, e.g., title compds. [I; R1 = alkyl, alkenyl, alkynyl, alkoxy, alkylthio, halo, R2-substituted Ph; R2, R3 = H, halo, OH, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, CF3, dialkylamino; X = O, S, CO, CH2; Y = O, CH2; XY = CH:CH, C.tplbond.C; Z = alkylene; A = bond, O, S, CH:CH, etc.; R4 = (substituted) (hetero)aryl; with provisos] for manuf. of a medicament for treating or preventing Alzheimer's disease is claimed. Thus, 5-hydroxybenzopyran-2-one and 3-(2-ethyl-4-(4-fluorophenyl)-5-benzyloxyphenyl)propyl iodide were stirred with NaH in Me2SO to give 5-[3-(2-ethyl-4-(4-fluorophenyl)-5-benzyloxyphenyl)propoxy]benzopyran-2-one. This was converted to title compd. (II), which displaced [3H]-LTB4 from guinea pig lung membrane prepns. with pKi = 9.01. I drug formulations are given.

REFERENCE 6

AN 124:55467 CA
TI Synthetic and Structure/Activity Studies on Acid-Substituted 2-Arylphenols: Discovery of 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]- propoxy]phenoxy]benzoic Acid, a High-Affinity Leukotriene B4 Receptor Antagonist
AU Sawyer, J. Scott; Bach, Nicholas J.; Baker, S. Richard; Baldwin, Ronald F.; Borromeo, Peter S.; Cockerham, Sandra L.; Fleisch, Jerome H.; Floreancig, Paul; Froelich, Larry L.; et al.
CS Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN,

46285, USA
SO Journal of Medicinal Chemistry (1995), 38(22), 4411-32
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB Structural derivs. of LY255283 have been studied as receptor antagonists of leukotriene B4. Substitution of the 2-hydroxyacetophenone subunit of 1-[5-Ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl]ethanone (LY255283) with a 2-arylphenol group provided entry into several new series that feature various mono- and diacidic core functionality. These new analogs, the subject of a broad structure-activity investigation, displayed significantly increased in vitro and in vivo activity as receptor antagonists of LTB4. A series of diaryl ether carboxylic acids demonstrated esp. interesting activity and led to the discovery of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid (LY293111), a 2-arylphenol-substituted diaryl ether carboxylic acid which displayed potent binding to human neutrophils (IC50 = 17 .+-. 4.6 nM) and guinea pig lung membranes (IC50 = 6.6 .+-. 0.71 nM), inhibition of LTB4-induced expression of the CD11b/CD18 receptor on human neutrophils (IC50 = 3.3 .+-. 0.81 nM), and inhibition of LTB4-induced contraction of guinea pig lung parenchyma (pKB = 8.7 .+-. 0.16). 801Vivo, LY293111 demonstrated potent activity in inhibiting LTB4-induced airway obstruction in the guinea pig when dosed by the oral (ED50 = 0.40 mg/kg) or i.v. (ED50 = 0.014 mg/kg) routes. A specific LTB4 receptor antagonist, LY293111 had little effect on inhibiting contractions of guinea pig lung parenchyma induced by leukotriene D4 (LTD4), histamine, carbachol, or U46619. LY293111 was chosen as a clin. candidate and is currently in phase I studies for a variety of inflammatory diseases.

REFERENCE 7

AN 120:244331 CA
TI Substituted phenyl phenol leukotriene antagonists
IN Baker, Stephen Richard; Dillard, Robert Delane; Floreancig, Paul Edward; Sawyer, Jason Scott; Schmittling, Elisabeth Andree; Sofia, Michael Joseph
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 119 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 544488	A2	19930602	EP 1992-310705	19921123
	EP 544488	A3	19930728		
	EP 544488	B1	19980311		
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	ZA 9209051	A	19940523	ZA 1992-9051	19921123
	HU 66023	A2	19940829	HU 1992-3666	19921123
	CZ 280133	B6	19951115	CZ 1992-3460	19921123
	CZ 280135	B6	19951115	CZ 1994-2766	19921123
	AT 163914	E	19980315	AT 1992-310705	19921123
	ES 2116324	T3	19980716	ES 1992-310705	19921123
	IL 116942	A1	20000229	IL 1992-116942	19921123
	IL 103847	A1	20000601	IL 1992-103847	19921123
	CA 2083639	AA	19930526	CA 1992-2083639	19921124
	NO 9204523	A	19930526	NO 1992-4523	19921124
	NO 180044	B	19961028		

	NO 180044	C	19970205		
	AU 9228573	A1	19930527	AU 1992-28573	19921124
	AU 658023	B2	19950330		
	BR 9204527	A	19930720	BR 1992-4527	19921124
	RU 2095340	C1	19971110	RU 1992-4509	19921124
	JP 05286852	A2	19931102	JP 1992-314973	19921125
	CN 1088906	A	19940706	CN 1993-100106	19930102
	CN 1035001	B	19970528		
	US 5462954	A	19951031	US 1994-333122	19941101
PRAI	US 1991-797522	19911125			
	US 1991-797646	19911125			
	IL 1992-103847	19921123			

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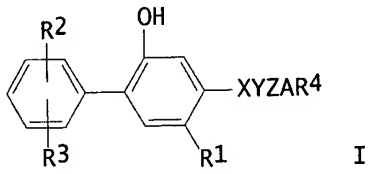

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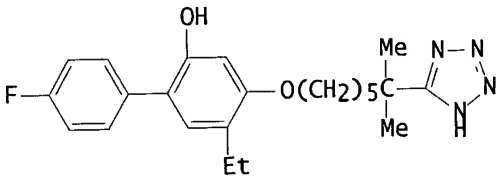
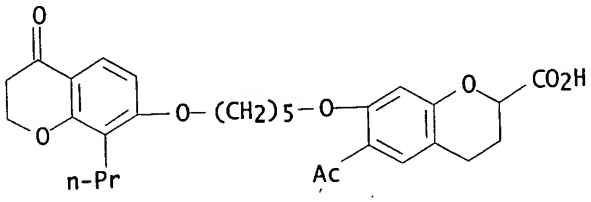


II

AB The title compds., 1,1'-biphenyl-2-ol derivs. I (R1 = alkyl, alkenyl, etc.; R2, R3 = H, alkyl, alkoxy, etc.; R4 = alkylsulfonyl, trifluoromethyl, alkylamino; X = oxygen, sulfur, methylene, carbonyl; Y = oxygen, methylene, etc.; S = bond, alkanediyl; Y = oxygen, sulfur, alkenediyl, etc.) and their uses as leukotriene antagonists are claimed. I are selective leukotriene B4 antagonists, i.e. they are useful as inflammation inhibitors, antiallergics, and antiasthmatics. Debenzylation of 2-methyl-2-(1H-tetrazol-5-yl)-7-[2-ethyl-4-(4-fluorophenyl)]-5-[(benzyloxy)phenoxy]heptane (prepd. in several steps) gave 2-methyl-2-(1H-tetrazol-5-yl)-7-[2-ethyl-4-(4-fluorophenyl)]-5-hydroxyphenoxyheptane (II), [i.e. 4-ethyl-3'-fluoro-5-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]-1,1'biphenyl-2-ol]. II inhibited leukotrienes B4 in pig lung membrane with a pKi of 8.52.

L10 ANSWER 10 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 150597-26-5 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 6-acetyl-7-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-3,4-dihydro- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1-Benzopyran-2-carboxylic acid, 6-acetyl-7-[[5-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]pentyl]oxy]-3,4-dihydro-, (.+-.)-
FS 3D CONCORD
MF C29 H34 O8
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

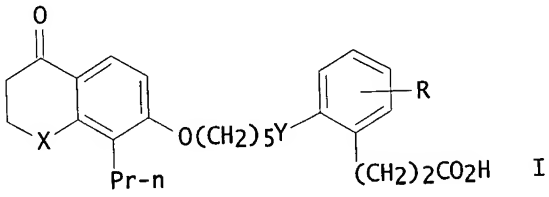


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:150847 CA
TI Benzenepropanoic acids containing chromanone or naphthalenone moieties are potent and orally active leukotriene B4 antagonists
AU Cohen, Noal; Bizzarro, Fred T.; May, William P.; Toth, Katherine; Lee, Ferdinand K.; Heslin, Peter H.; Holland, George W.; Kwoh, Shuan C.; Franco, Lucia S.; et al.
CS Roche Research Center, Hoffmann-La Roche, Inc., Nutley, NY, 07110, USA
SO Bioorganic & Medicinal Chemistry Letters (1994), 4(24), 2883-8
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
GI



I

AB Systematic structural modification of peptidoleukotriene antagonists of the o-hydroxyacetophenone class has led to the discovery of certain [[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]alkyl]benzenepropanoic acids and related compds. I (X and Y = O OR CH2, R = H or [O(CH2)nCO2H, n = 3-8]), which appear to be potent and selective antagonists of the proinflammatory mediator leukotriene B4. The compds. were tested for inhibition of leukotriene B4 binding in human neutrophils and as antagonists of leukotriene B4-induced bronchoconstriction in guinea pigs.

REFERENCE 2

AN 119:225820 CA
TI Preparation of benzopyranonecarboxylic acid derivatives as antiinflammatants
IN Cohen, Noal; Lee, Ferdinand Kwo Chen; Yagaloff, Keith Alan
PA Hoffmann-La Roche, F., und Co. A.-G., Switz.

SO Eur. Pat. Appl., 128 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 531823	A1	19930317	EP 1992-114691	19920828
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	US 5273999	A	19931228	US 1992-898852	19920615
	RU 2067973	C1	19961020	RU 1992-5052388	19920828
	CA 2077213	AA	19930311	CA 1992-2077213	19920831
	HU 66238	A2	19941028	HU 1992-2817	19920902
	ZA 9206691	A	19930310	ZA 1992-6691	19920903
	AU 9222191	A1	19930311	AU 1992-22191	19920907
	AU 655057	B2	19941201		
	NO 9203508	A	19930311	NO 1992-3508	19920909
	CN 1071423	A	19930428	CN 1992-111386	19920909
	JP 05201915	A2	19930810	JP 1992-266694	19920909
	BR 9203508	A	19930413	BR 1992-3508	19920910
	US 5434186	A	19950718	US 1993-128612	19930928
PRAI	US 1991-757100		19910910		
	US 1992-898852		19920615		

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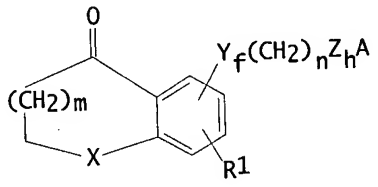


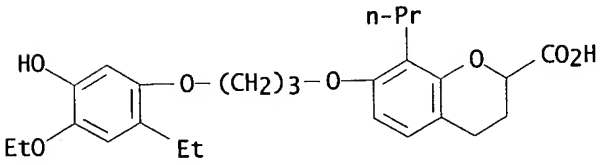
I

AB Title compds. [I; X = O, CH2; Y = O, CH2CH2, CH:CH, C.tplbond.C, OCH2C6H4; Z = CH2CH2, CH:CH, C.tplbond.C; R1 = H, alkyl, alkenyl, cycloalkyl, aralkyl; A = B, OB; B = substituted mono-, bi-, or tricyclic (hetero)aryl; h, m = 0, 1; n = 1-12], were prepd. as LTB4 antagonists. Thus, 2,3-dihydro-7-hydroxy-8-propyl-4H-1-benzopyran-4-one (prepn. given) was alkylated with Me 2-[(6-methoxy-6-oxohexyl)oxy]-6-[6-(methylsulfonyl)oxyhexyl]benzenepropanoate (prepn. given) followed by sapon. to give 2-[(5-carboxypentyl)oxy]-6-[6-[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]hexyl]benzenepropanoic acid (II). II inhibited LTB4-induced bronchoconstriction with ID50 = 0.07 mg/kg i.v. Dosage forms were prepd. contg. II.

=> d l10 ide bib abs 11-27

L10 ANSWER 11 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 147612-00-8 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-(4-ethoxy-2-ethyl-5-hydroxyphenoxy)propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN LY 282201
FS 3D CONCORD
MF C26 H34 O7
SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1957 TO DATE)
7 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 134:371777 CA
TI Oncolytic combinations of radiotherapy and leukotriene B4 antagonists for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034199	A2	20010517	WO 2000-US30982	20001109
	WO 2001034199	A3	20020307		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164902P 19991111
AB A method of treating cancer with radiation, in conjunction with the administration of a leukotriene (LTB4) antagonist is disclosed. Capsules were prepd. contg. 1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-.alpha.,.alpha.-dimethyl-5-(1-methylethyl)-1H-indole-2-propanoic acid.

REFERENCE 2

AN 134:371774 CA
TI Oncolytic combinations of antitumor agents and leukotriene antagonists for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034133	A2	20010517	WO 2000-US30892	20001109
	WO 2001034133	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164705P 19991111

AB The therapeutic combinations of leukotriene (LTB4) inhibitors and anti-cancer agents are disclosed. A method of treating cancer using leukotriene (LTB4) inhibitors in conjunction with anti-cancer agents is also disclosed.

REFERENCE 3

AN 134:357589 CA

TI Pharmaceutical preparations containing synergistic oncolytic combinations for the treatment of cancer

IN Sawyer, Jason Scott; Teicher, Beverly Ann; Benjamin, Roger Stuart

PA Eli Lilly and Company, USA

SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034134	A2	20010517	WO 2000-US30894	20001109
	WO 2001034134	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164716P 19991111

AB Leukotriene (LTB4) antagonists enhance the effectiveness of 2',2'-difluoronucleoside anti-cancer agents. A capsule contained LTB4 antagonist (CP-195543) 25, gemcitabine hydrochloride (I) 225, starch 200, and magnesium stearate 10 mg. Efficacy of CP-195543 in enhancing oncolytic activity of I in mice was shown.

REFERENCE 4

AN 132:246369 CA

TI Use of non-peptidyl compounds for the treatment of insulin-related ailments

IN Helmerhorst, Erik; Plewright, Brian Scott

PA Curtin University of Technology, Australia

SO PCT Int. Appl., 129 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000016798	A1	20000330	WO 1999-AU786	19990917
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2345155	AA	20000330	CA 1999-2345155	19990917
AU 9960707	A1	20000410	AU 1999-60707	19990917
EP 1115422	A1	20010718	EP 1999-947113	19990917
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI AU 1998-6091 19980922
WO 1999-AU786 19990917

AB The present invention relates to the use of at least a non-peptidyl compd. as a biol. modulator of insulin activity or insulin-related activity for the treatment of insulin-related diseases. Non-peptidyl compds. of the present invention exert their effects by mimicking amino acids spatially located on insulin, enabling those compds. to bind to the insulin receptor or insulin-like receptor causing biol. modulation of the activity of the receptor. A method for identifying a non-peptidyl compd. comprises the steps of: (1) comparing the 3D structure of the non-peptidyl compd. with a 3D pharmacophore of an active site of insulin, and (2) selecting a non-peptidyl compd. The compds. may act either as agonists or antagonists of insulin or insulin-like activity. Pharmaceutical compns. contg. chem. compds. capable of modulating the biol. activity of insulin are also claimed. For example, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (IM 025) was an antagonist of insulin action. IM 025 caused a dose-dependent decrease in the incorporation of 32P into FYF peptide in insulin-stimulated tubes and inhibited glucose transport in 3T3L1 cells, with IC50 of 150 and 170 .mu.M, resp. 2,4-Dichloro-6-[N-(trifluoromethanesulfonyl)sulfamoylphenyl-3,5-dichloro-2-hydroxybenzene] sulfonate (IM 103) was an agonist of insulin action displaying a biphasic biol. dose response curve with an apex at concn. of 110 .mu.M and an apparent EC50 of 45 .+-. 7 .mu.M.

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 5

AN 123:188623 CA
TI Use of PLA2 inhibitors as treatment for Alzheimers disease
IN Clemens, James Allen; Sofia, Michael Joseph; Stepenson, Diane Teresa
PA Lilly, Eli, and Co., USA
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9517183	A1	19950629	WO 1994-US14504	19941214

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RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	US 5478857	A	19951226	US 1993-173544	19931223
	CA 2179649	AA	19950629	CA 1994-2179649	19941214
	AU 9514028	A1	19950710	AU 1995-14028	19941214
	AU 688446	B2	19980312		
	EP 735870	A1	19961009	EP 1995-905404	19941214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CN 1142768	A	19970212	CN 1994-195027	19941214
	HU 75335	A2	19970528	HU 1996-1741	19941214
	JP 09507069	T2	19970715	JP 1994-517514	19941214
	BR 9408407	A	19970805	BR 1994-8407	19941214
	ZA 9410041	A	19960618	ZA 1994-10041	19941215
	US 5563164	A	19961008	US 1995-464030	19950605
	NO 9602568	A	19960809	NO 1996-2568	19960617
	FI 9602557	A	19960822	FI 1996-2557	19960619
PRAI	US 1993-173544	19931223			
	WO 1994-US14504	19941214			

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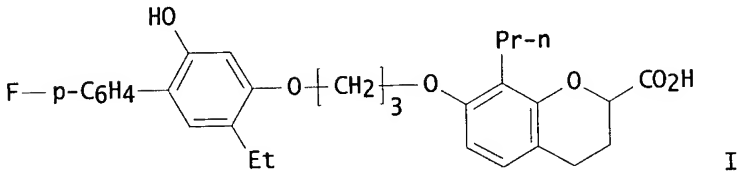

I

AB This invention provides methods for the treatment or prevention of Alzheimer's disease in a mammal which comprises administering to a mammal in need thereof an effective amt. of an inhibitor of phospholipase A2 (PLA2), esp. cytosolic PLA2. E.g., I was prepd. and shows good PLA2 inhibitory activity. Pharmaceutical formulations are also given.

REFERENCE 6

AN 120:322935 CA
TI Preparation of 1,2,4-trihydroxybenzene derivatives as leukotriene antagonists
IN Sofia, Michael Joseph
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 53 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 579412	A1	19940119	EP 1993-305090	19930629
	EP 579412	B1	19981007		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				

	US 5352690	A	19941004	US 1992-907492	19920701
	CA 2095487	AA	19940102	CA 1993-2095487	19930504
	JP 06080566	A2	19940322	JP 1993-154990	19930625
	ES 2121949	T3	19981216	ES 1993-305090	19930629
PRAI	US 1992-907492	19920701			

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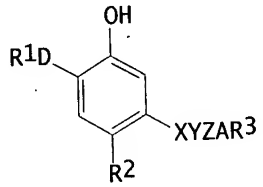

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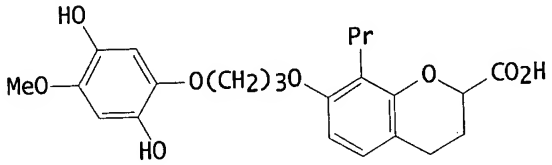


II

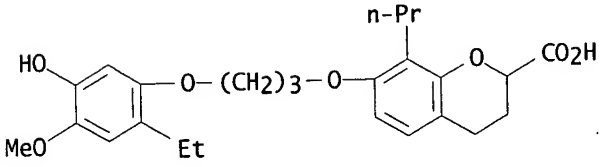
AB Title compds. [I; A = bond, O, S, CH:CH, etc.; D = O or S; R1 = (cyclo)alkyl, (substituted)Ph; R2 = alk(en)yl, alkynyl, alkoxy; R3 = CO2H, tetrazol-5-yl, etc.; X = O, S, CO, CH2; Y = O, CH2; XY = CH:CH, C.tplbond.C; Z = bond, alkylidenyl(sic)] were prepd. Thus, 5-ethyl-2,4-dihydroxybenzaldehyde was condensed with Et 3,4-dihydro-7-[1-(3-hydroxypropropoxy)]-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. each given) and the product converted in 5 steps to title compd. II which had IC50 of 2.9nM against LTB4 binding to human neutrophils in vitro.

REFERENCE 7

AN 118:233824 CA
TI Ortho-alkoxyphenyl leukotriene B4 receptor antagonists: effect of a chromancarboxylic acid
AU Sofia, Michael J.; Saussy, David L., Jr.; Jackson, William T.; Marder, Philip; Silbaugh, Steven A.; Froelich, Larry L.; Cockerham, Sandra L.; Stengel, Peter W.
CS Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Bioorganic & Medicinal Chemistry Letters (1992), 2(12), 1675-80
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Several o-alkoxyphenols contg. a chroman carboxylic acid side-chain have been prepd. as antagonists of leukotriene B4 receptors. These antagonists were compared to their parent alkoxyphenols contg. the tetrazole acid side-chain. These chroman contg. antagonists retained their binding potency for human neutrophil receptors; however, showed enhanced potency against guinea pig receptors in both in vitro and in vivo systems.

L10 ANSWER 12 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 147611-93-6 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-(2-ethyl-5-hydroxy-4-methoxyphenoxy)propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD

MF C25 H32 O7
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 120:322935 CA
TI Preparation of 1,2,4-trihydroxybenzene derivatives as leukotriene antagonists
IN Sofia, Michael Joseph
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 53 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 579412	A1	19940119	EP 1993-305090	19930629
	EP 579412	B1	19981007		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	US 5352690	A	19941004	US 1992-907492	19920701
	CA 2095487	AA	19940102	CA 1993-2095487	19930504
	JP 06080566	A2	19940322	JP 1993-154990	19930625
	ES 2121949	T3	19981216	ES 1993-305090	19930629
PRAI	US 1992-907492		19920701		

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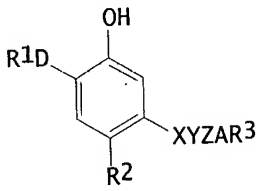

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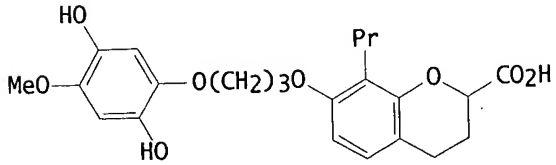


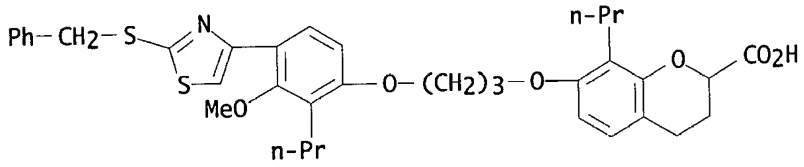
II

AB Title compds. [I; A = bond, O, S, CH:CH, etc.; D = O or S; R1 = (cyclo)alkyl, (substituted)Ph; R2 = alk(en)yl, alkynyl, alkoxy; R3 = CO2H, tetrazol-5-yl, etc.; X = O, S, CO, CH2; Y = O, CH2; XY = CH:CH, C.tplbond.C; Z = bond, alkylidenyl(sic)] were prepd. Thus, 5-ethyl-2,4-dihydroxybenzaldehyde was condensed with Et 3,4-dihydro-7-[1-(3-hydroxypropropoxy)]-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. each given) and the product converted in 5 steps to title compd. II which had IC50 of 2.9nM against LTB4 binding to human neutrophils in vitro.

REFERENCE 2

AN 118:233824 CA
TI Ortho-alkoxyphenyl leukotriene B4 receptor antagonists: effect of a chromancarboxylic acid
AU Sofia, Michael J.; Saussy, David L., Jr.; Jackson, William T.; Marder, Philip; Silbaugh, Steven A.; Froelich, Larry L.; Cockerham, Sandra L.; Stengel, Peter W.
CS Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Bioorganic & Medicinal Chemistry Letters (1992), 2(12), 1675-80
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Several o-alkoxyphenols contg. a chroman carboxylic acid side-chain have been prepd. as antagonists of leukotriene B4 receptors. These antagonists were compared to their parent alkoxyphenols contg. the tetrazole acid side-chain. These chroman contg. antagonists retained their binding potency for human neutrophil receptors; however, showed enhanced potency against guinea pig receptors in both in vitro and in vivo systems.

L10 ANSWER 13 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-47-4 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-4-[2-[(phenylmethyl)thio]-4-thiazolyl]-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C36 H41 N O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930:

Heterocyclic Replacement of the Methyl Ketone Pharmacophore

AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.

CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA

SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:83676 CA

TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists

IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick

PA Searle, G. D., and Co., USA

SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
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	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501
	AU 647487	B2	19940324		
	EP 527922	A1	19930224	EP 1991-910026	19910501
	EP 527922	B1	19950308		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05507084	T2	19931014	JP 1991-509388	19910501
	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913

	US 5212198	A 19930518	US 1992-958632	19921009
PRAI	US 1990-521777	19900510		
	WO 1991-US2981	19910501		
	US 1991-759272	19910913		

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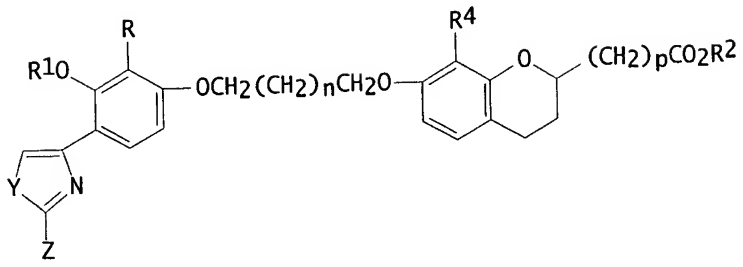
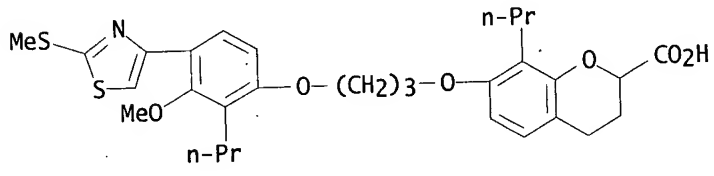


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 14 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-46-3 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-4-[2-(methylthio)-4-thiazolyl]-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H37 N O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
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	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501
	AU 647487	B2	19940324		
	EP 527922	A1	19930224	EP 1991-910026	19910501
	EP 527922	B1	19950308		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				

	JP 05507084	T2	19931014	JP 1991-509388	19910501
	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
PRAI	US 1990-521777	19900510			
	WO 1991-US2981	19910501			
	US 1991-759272	19910913			

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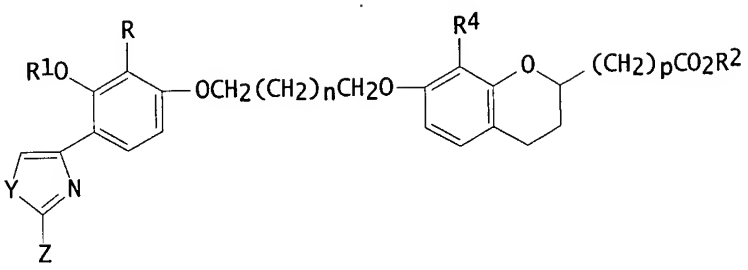

I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 15 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-44-1 REGISTRY
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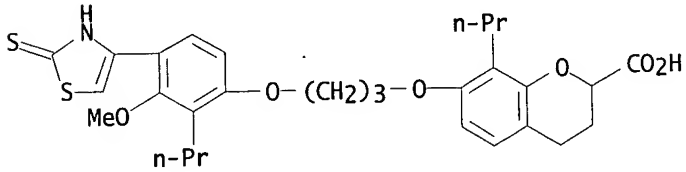
MF C29 H35 N O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501

	AU 9179020	A1	19911127	AU 1991-79020 19910501
	AU 647487	B2	19940324	
	EP 527922	A1	19930224	EP 1991-910026 19910501
	EP 527922	B1	19950308	
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	JP 05507084	T2	19931014	JP 1991-509388 19910501
	ES 2069295	T3	19950501	ES 1991-910026 19910501
	IL 98090	A1	19950731	IL 1991-98090 19910509
	ZA 9103546	A	19920729	ZA 1991-3546 19910510
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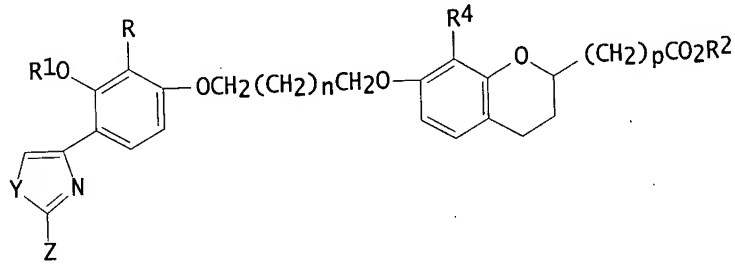

I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 16 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-42-9 REGISTRY
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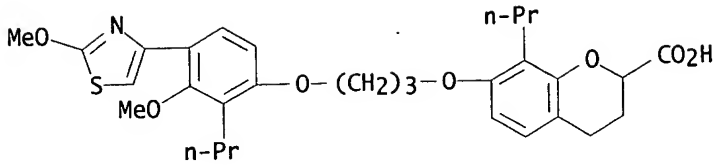
FS 3D CONCORD
MF C30 H37 N O7 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



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2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
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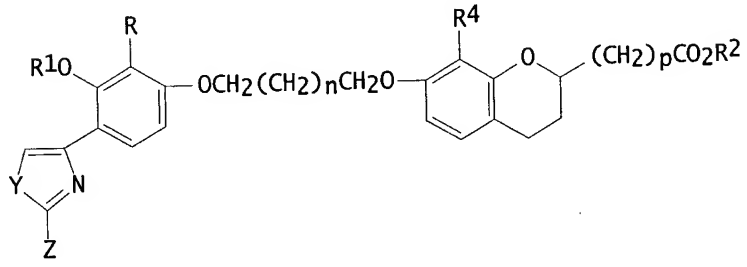
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501
	AU 647487	B2	19940324		
	EP 527922	A1	19930224	EP 1991-910026	19910501
	EP 527922	B1	19950308		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05507084	T2	19931014	JP 1991-509388	19910501
	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
PRAI	US 1990-521777	19900510			
	WO 1991-US2981	19910501			
	US 1991-759272	19910913			

GI

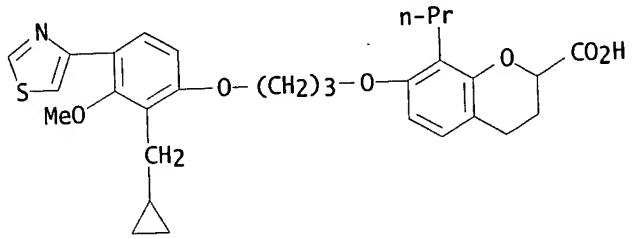


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 17 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-39-4 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)
OTHER NAMES:

CN SC 50605
FS 3D CONCORD
MF C30 H35 N O6 S
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CIN, EMBASE, MEDLINE, PHAR, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10 REFERENCES IN FILE CA (1957 TO DATE)
10 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 137:346175 CA
TI Use of lipoxygenase inhibitors for the treatment of acne
IN Zouboulis, Christos C.
PA Germany
SO Ger. Offen., 6 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10121252	A1	20021107	DE 2001-10121252	20010430
	WO 2002089791	A2	20021114	WO 2002-EP4715	20020429

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI DE 2001-10121252 20010430
AB The invention discloses the use of lipoxygenase inhibitors for the treatment of acne, in particular inflammatory acne. The lipoxygenase inhibitor can be used alone or into combination with other lipoxygenase inhibitors or with further anti-acne agents in a suitable pharmaceutical compn., in particular via oral and/or local topical application.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE 2

AN 134:371777 CA
TI Oncolytic combinations of radiotherapy and leukotriene B4 antagonists for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034199	A2	20010517	WO 2000-US30982	20001109
	WO 2001034199	A3	20020307		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164902P 19991111
AB A method of treating cancer with radiation, in conjunction with the administration of a leukotriene (LTB4) antagonist is disclosed. Capsules were prepd. contg. 1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-.alpha.,.alpha.-dimethyl-5-(1-methylethyl)-1H-indole-2-propanoic acid.

REFERENCE 3

AN 134:371774 CA
TI Oncolytic combinations of antitumor agents and leukotriene antagonists for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034133	A2	20010517	WO 2000-US30892	20001109
	WO 2001034133	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164705P 19991111
AB The therapeutic combinations of leukotriene (LTB4) inhibitors and anti-cancer agents are disclosed. A method of treating cancer using leukotriene (LTB4) inhibitors in conjunction with anti-cancer agents is also disclosed.

REFERENCE 4

AN 134:357589 CA
TI Pharmaceutical preparations containing synergistic oncolytic combinations for the treatment of cancer
IN Sawyer, Jason Scott; Teicher, Beverly Ann; Benjamin, Roger Stuart
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001034134	A2	20010517	WO 2000-US30894	20001109
	WO 2001034134	A3	20020214		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-164716P 19991111
AB Leukotriene (LTB4) antagonists enhance the effectiveness of 2',2'-difluoronucleoside anti-cancer agents. A capsule contained LTB4 antagonist (CP-195543) 25, gemcitabine hydrochloride (I) 225, starch 200, and magnesium stearate 10 mg. Efficacy of CP-195543 in enhancing oncolytic activity of I in mice was shown.

REFERENCE 5

AN 124:232451 CA
TI Preparation of (azolylphenoxy)alkoxy-substituted dihydrobenzopyran-2-sulfonimides derivatives as leukotriene B4 antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale
PA G.D. Searle and Co., USA
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9532201	A1	19951130	WO 1995-US5850	19950517

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	AU 9525855	A1	19951218	AU 1995-25855	19950517
	US 5578619	A	19961126	US 1995-569323	19951208

PRAI US 1994-249107 19940525
WO 1995-US5850 19950517
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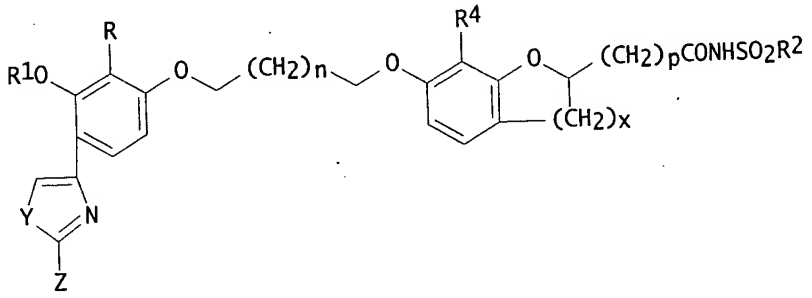

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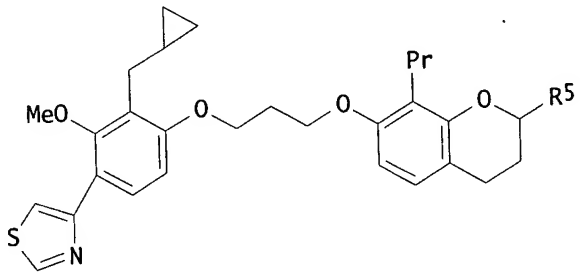


II

AB The title compds. [I; R = C2-6 alkyl, alkenyl, or alkynyl, (CH2)mR3; wherein R3 = C3-5 cycloalkyl; m = 1 or 2; R1 = C1-4 alkyl; R2 = C1-5 alkyl, aryl optionally substituted with halogen or C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; x = 0 or 2; Y = NH, O, S; Z = H, C1-4 alkyl or alkoxy] and stereoisomers and pharmaceutically acceptable salts thereof, which are useful as antiinflammatory agents and in the treatment of leukotriene B4 mediated conditions such as inflammatory diseases including rheumatoid arthritis, psoriasis, inflammatory bowel disease, gout, asthma, and multiple sclerosis, are prepd. Thus, the benzopyrancarboxylic acid deriv. (II; R = CO2H) 15, PhSO2NH2 15, 4-dimethylaminopyridine 15, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide 19 mg, and 5 mL CH2Cl2 were stirred with 4.ANG. mol. sieves at room temp. for 24 h to give, after flash chromatog., 29 mg the Ph sulfonimide II (R = CONHSO2Ph). The latter compd. and II (R = CH2CH2CONHSO2Ph) showed the leukotriene B4 receptor binding affinity 5.5 and 4.3 times, resp., greater than that of 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid.

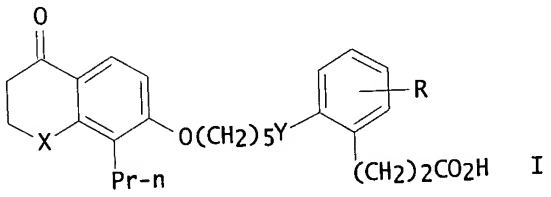
REFERENCE 6

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal

LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 7

AN 122:150847 CA
TI Benzenepropanoic acids containing chromanone or naphthalenone moieties are potent and orally active leukotriene B4 antagonists
AU Cohen, Noal; Bizzarro, Fred T.; May, William P.; Toth, Katherine; Lee, Ferdinand K.; Heslin, Peter H.; Holland, George W.; Kwoh, Shuan C.; Franco, Lucia S.; et al.
CS Roche Research Center, Hoffmann-La Roche, Inc., Nutley, NY, 07110, USA
SO Bioorganic & Medicinal Chemistry Letters (1994), 4(24), 2883-8
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
GI



I

AB Systematic structural modification of peptidoleukotriene antagonists of the o-hydroxyacetophenone class has led to the discovery of certain [[(3,4-dihydro-4-oxo-8-propyl-2H-1-benzopyran-7-yl)oxy]alkyl]benzenepropanoic acids and related compds. I (X and Y = O OR CH2, R = H or [O(CH2)nCO2H, n = 3-8]), which appear to be potent and selective antagonists of the proinflammatory mediator leukotriene B4. The compds. were tested for inhibition of leukotriene B4 binding in human neutrophils and as antagonists of leukotriene B4-induced bronchoconstriction in guinea pigs.

REFERENCE 8

AN 120:68854 CA
TI The design and synthesis of second generation leukotriene B4 (LTB4)

receptor antagonists related to SC-41930

AU Penning, T. D.; Djuric, S. W.; Docter, S. H.; Yu, S. S.; Spangler, D.; Anglin, C. P.; Fretland, D. J.; Kachur, J. F.; Kieth, R. H.; et al.

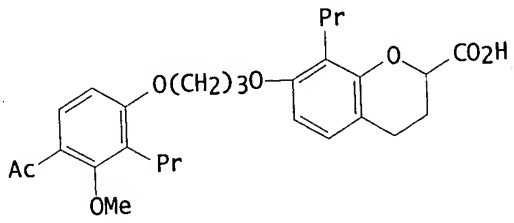
CS Dep. Chem., Searle Res. Dev., Skokie, IL, 60077, USA

SO Agents and Actions (1993), 39(Spec. Conf. Issue), C11-C13
CODEN: AGACBH; ISSN: 0065-4299

DT Journal

LA English

GI



I

AB SC-41930 (I) is a selective, orally active, LTB4 receptor antagonist currently in clin. trials for psoriasis and ulcerative colitis. Exhaustive SAR studies found a potential backup compd., SC-50605, which was 7-16 times more potent that SC-50605 also inhibited LTB4-induced intradermal chemotaxis in cavine skin at an oral dose of 0.10 mg/kg and displayed good activity in animal models of colitis and epidermal inflammation both orally and topically.

REFERENCE 9

AN 119:195290 CA

TI Leukotriene B4-induced granulocyte trafficking in guinea pig dermis: effect of second-generation leukotriene B4 receptor antagonists, SC-50605 and SC-51146

AU Fretland, D. J.; Widomski, D. L.; Anglin, C. P.; Penning, T. D.; Yu, S.; Djuric, S. W.

CS Dep. Immunoinflammat. Dis. Res., Skokie, IL, 60077, USA

SO Inflammation (New York, NY, United States) (1993), 17(3), 353-60
CODEN: INFLD4; ISSN: 0360-3997

DT Journal

LA English

AB Leukotriene B4 (LTB4) is a proinflammatory product of arachidonic acid metab. that has been implicated as a mediator in a no. of inflammatory diseases. When injected intradermally into the guinea pig, LTB4 elicits a dose-dependent migration (chemotaxis) of neutrophils (PMNs) into the injection sites as assessed by the presence of a neutrophil marker enzyme myeloperoxidase. SC-41930 {7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid}, a first-generation LTB4 receptor antagonist inhibited the chemotactic actions of LTB4 when coadministered into the dermal site and when given orally with ED50 values of 340 ng and 1.7 mg/kg, resp. The second-generation LTB4 receptor antagonists SC-50605 {7-[3-2(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid} and SC-51146 {7-[3-[2(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid} inhibited LTB4-induced chemotaxis when coadministered with ED50 values of 70 ng and 32 ng, resp., and when given intragastrically with ED50 values of 0.10 and 0.09 mg/kg, resp. SC-41930, SC-50605, and SC-51146 had oral durations of

action of 5.5, 15, and 21 h, resp. These potent, LTB4 receptor antagonists may well have application in the medical management of disease states such as asthma, rheumatoid arthritis, inflammatory bowel disease, contact dermatitis, and psoriasis, where LTB4 is implicated as an inflammatory mediator.

REFERENCE 10

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501
	AU 647487	B2	19940324		
	EP 527922	A1	19930224	EP 1991-910026	19910501
	EP 527922	B1	19950308		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05507084	T2	19931014	JP 1991-509388	19910501
	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
PRAI	US 1990-521777	19900510			
	WO 1991-US2981	19910501			
	US 1991-759272	19910913			

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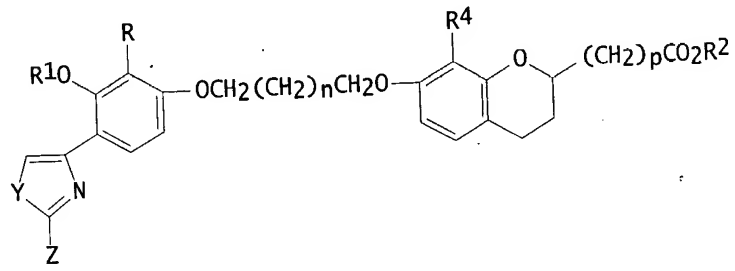
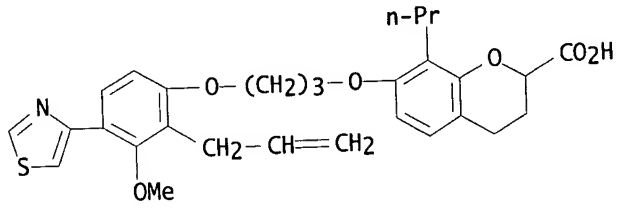


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H,

PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 18 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-36-1 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-2-(2-propenyl)-4-(4-thiazolyl)phenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SC 50606
FS 3D CONCORD
MF C29 H33 N O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

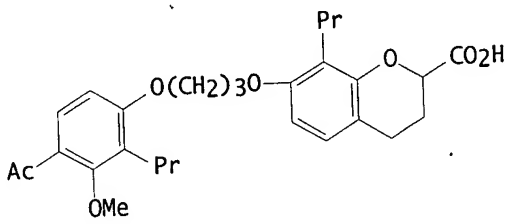
REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605

(7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 120:68854 CA
TI The design and synthesis of second generation leukotriene B4 (LTB4) receptor antagonists related to SC-41930
AU Penning, T. D.; Djuric, S. W.; Docter, S. H.; Yu, S. S.; Spangler, D.; Anglin, C. P.; Fretland, D. J.; Kachur, J. F.; Kieth, R. H.; et al.
CS Dep. Chem., Searle Res. Dev., Skokie, IL, 60077, USA
SO Agents and Actions (1993), 39(Spec. Conf. Issue), C11-C13
CODEN: AGACBH; ISSN: 0065-4299
DT Journal
LA English
GI



I

AB SC-41930 (I) is a selective, orally active, LTB4 receptor antagonist currently in clin. trials for psoriasis and ulcerative colitis. Exhaustive SAR studies found a potential backup compd., SC-50605, which was 7-16 times more potent that SC-50605 also inhibited LTB4-induced intradermal chemotaxis in cavine skin at an oral dose of 0.10 mg/kg and displayed good activity in animal models of colitis and epidermal inflammation both orally and topically.

REFERENCE 3

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501

W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR,

LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG

US 5073562	A	19911217	US 1990-521777	19900510
CA 2082500	AA	19911111	CA 1991-2082500	19910501
AU 9179020	A1	19911127	AU 1991-79020	19910501
AU 647487	B2	19940324		
EP 527922	A1	19930224	EP 1991-910026	19910501
EP 527922	B1	19950308		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE

JP 05507084	T2	19931014	JP 1991-509388	19910501
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IL 98090	A1	19950731	IL 1991-98090	19910509
ZA 9103546	A	19920729	ZA 1991-3546	19910510
US 5192782	A	19930309	US 1991-759272	19910913
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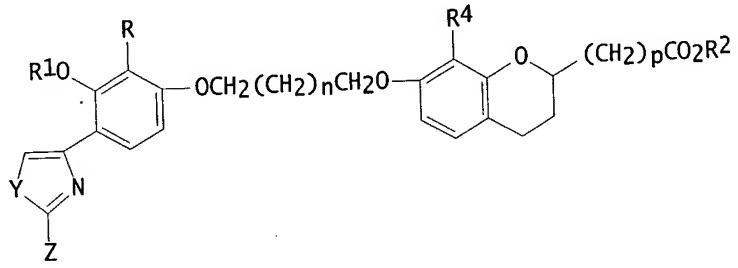

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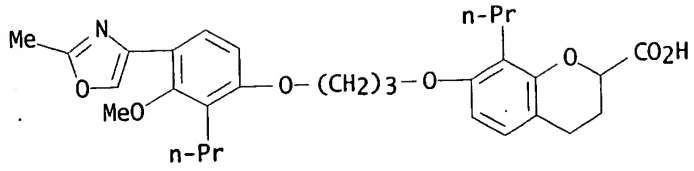
L10 ANSWER 19 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-33-8 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-4-(2-methyl-4-oxazolyl)-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H37 N O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
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AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
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DT Journal
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IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

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PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
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	AU 647487	B2	19940324		
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	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
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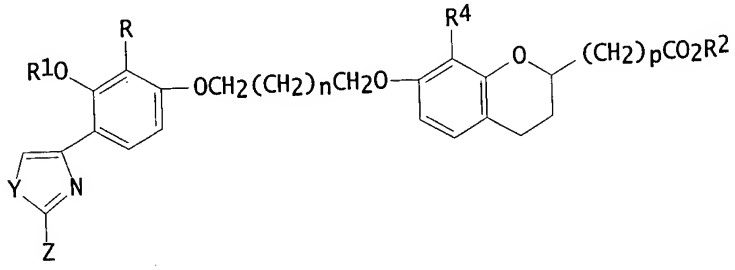

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L10 ANSWER 20 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-31-6 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-2-propyl-4-(4-thiazolyl)phenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
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CN SC 50210
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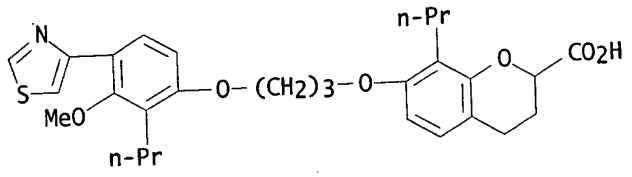

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

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CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
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REFERENCE 2

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AU Penning, T. D.; Djuric, S. W.; Docter, S. H.; Yu, S. S.; Spangler, D.;

Anglin, C. P.; Fretland, D. J.; Kachur, J. F.; Kieth, R. H.; et al.
CS Dep. Chem., Searle Res. Dev., Skokie, IL, 60077, USA
SO Agents and Actions (1993), 39(Spec. Conf. Issue), C11-C13
CODEN: AGACBH; ISSN: 0065-4299
DT Journal
LA English
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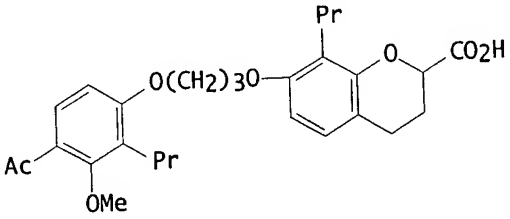

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PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
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	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
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	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501
	AU 647487	B2	19940324		
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	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
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WO 1991-US2981 19910501
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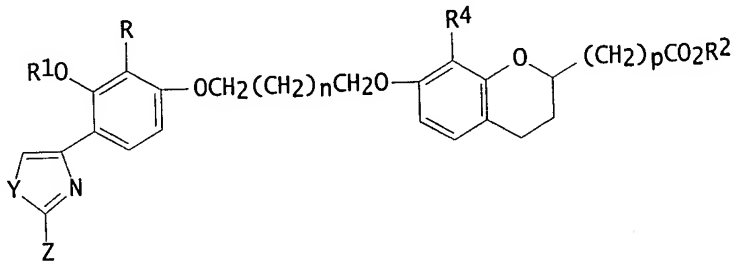

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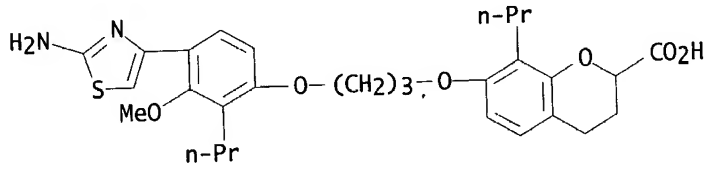
L10 ANSWER 21 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-29-2 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[3-[4-(2-amino-4-thiazolyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C29 H36 N2 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

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CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA

SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

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PA Searle, G. D., and Co., USA

SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

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	US 5073562	A	19911217	US 1990-521777	19900510
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	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913

	US 5212198	A 19930518	US 1992-958632	19921009
PRAI	US 1990-521777	19900510		
	WO 1991-US2981	19910501		
	US 1991-759272	19910913		

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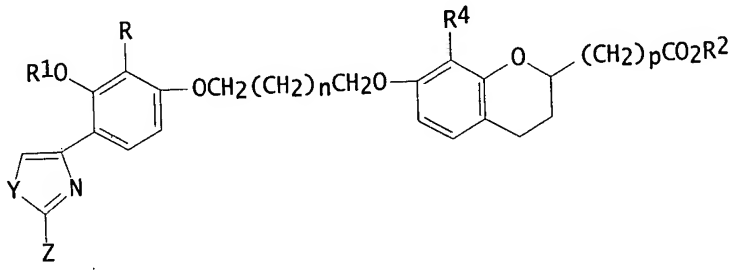
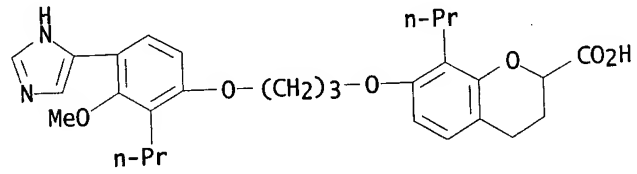


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 22 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-28-1 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[4-(1H-imidazol-4-yl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C29 H36 N2 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
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	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501
	AU 647487	B2	19940324		
	EP 527922	A1	19930224	EP 1991-910026	19910501
	EP 527922	B1	19950308		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
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	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
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	WO 1991-US2981	19910501			
	US 1991-759272	19910913			

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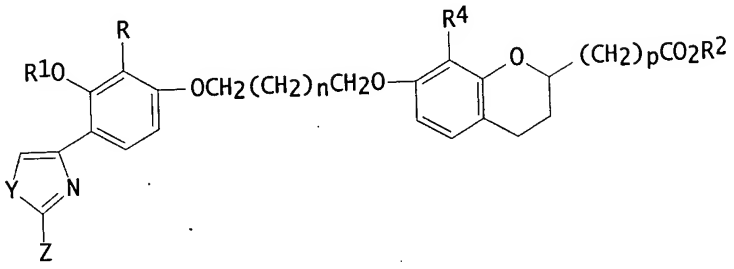
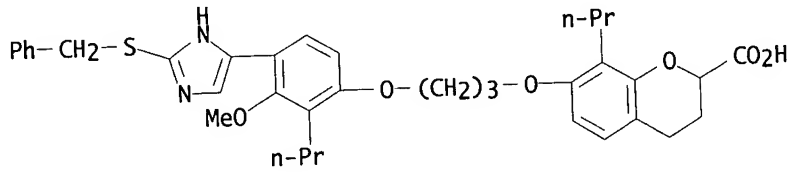


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 23 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-27-0 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-4-[2-[(phenylmethyl)thio]-1H-imidazol-4-yl]-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C36 H42 N2 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
	AU 9179020	A1	19911127	AU 1991-79020	19910501

	AU 647487	B2	19940324		
	EP 527922	A1	19930224	EP 1991-910026	19910501
	EP 527922	B1	19950308		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05507084	T2	19931014	JP 1991-509388	19910501
	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
PRAI	US 1990-521777	19900510			
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	US 1991-759272	19910913			

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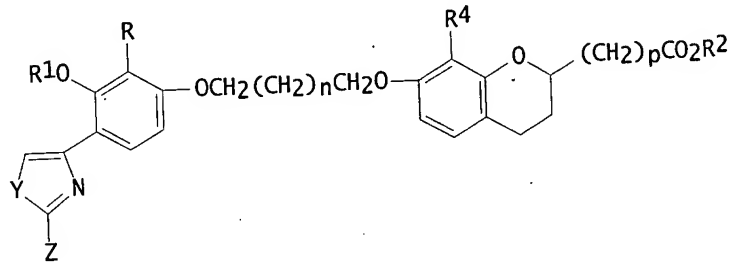
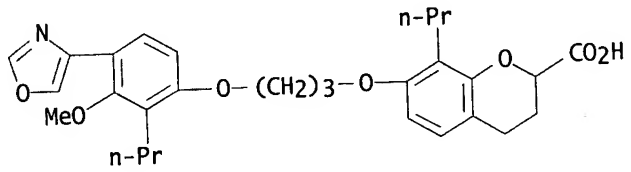


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl, R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 24 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 138828-24-7 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-4-(4-oxazolyl)-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN SC 49844
FS 3D CONCORD
MF C29 H35 N O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

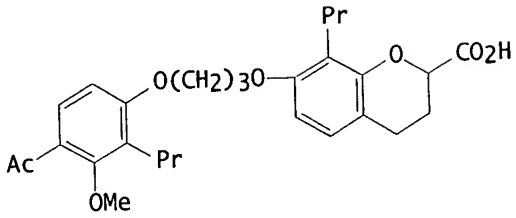
REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 120:68854 CA
TI The design and synthesis of second generation leukotriene B4 (LTB4) receptor antagonists related to SC-41930
AU Penning, T. D.; Djuric, S. W.; Docter, S. H.; Yu, S. S.; Spangler, D.; Anglin, C. P.; Fretland, D. J.; Kachur, J. F.; Kieth, R. H.; et al.
CS Dep. Chem., Searle Res. Dev., Skokie, IL, 60077, USA
SO Agents and Actions (1993), 39(Spec. Conf. Issue), C11-C13
CODEN: AGACBH; ISSN: 0065-4299
DT Journal
LA English

GI



I

AB SC-41930 (I) is a selective, orally active, LTB4 receptor antagonist currently in clin. trials for psoriasis and ulcerative colitis. Exhaustive SAR studies found a potential backup compd., SC-50605, which was 7-16 times more potent that SC-50605 also inhibited LTB4-induced intradermal chemotaxis in cavine skin at an oral dose of 0.10 mg/kg and displayed good activity in animal models of colitis and epidermal inflammation both orally and topically.

REFERENCE 3

AN 116:83676 CA
TI Preparation of heterocycles containing alkoxy-substituted dihydrobenzopyran-2-carboxylic acids as leukotriene B4 (LTB4) antagonists
IN Djuric, Stevan Wakefield; Penning, Thomas Dale; Snyder, James Patrick
PA Searle, G. D., and Co., USA
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9117160	A1	19911114	WO 1991-US2981	19910501
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	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	US 5073562	A	19911217	US 1990-521777	19900510
	CA 2082500	AA	19911111	CA 1991-2082500	19910501
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	AU 647487	B2	19940324		
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	JP 05507084	T2	19931014	JP 1991-509388	19910501
	ES 2069295	T3	19950501	ES 1991-910026	19910501
	IL 98090	A1	19950731	IL 1991-98090	19910509
	ZA 9103546	A	19920729	ZA 1991-3546	19910510
	US 5192782	A	19930309	US 1991-759272	19910913
	US 5212198	A	19930518	US 1992-958632	19921009
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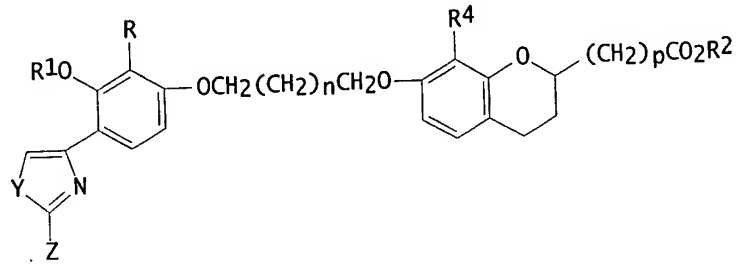
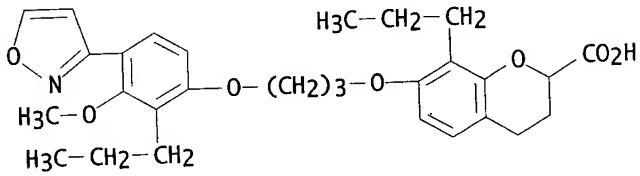


I

AB Title compds. I (R = C2-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, R3(CH2)m, wherein R3 = C3-5 cycloalkyl, m = 1,2; R1 = C1-4 alkyl; R2 = H, C1-5 alkyl; R4 = C1-6 alkyl; n = 1-5; p = 0-6; Y = NH, O, S; Z = H, C1-4 alkyl, C1-4 alkoxy, R5R4N wherein R4, R5 = H, C1-4 alkyl; R6S wherein R6 = H, PhCH2, C1-4 alkyl), stereoisomers and salts thereof, are prepd. I as LTB4 antagonists are useful as antiinflammatory agents and in treatment of LTB4-mediated conditions. The 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (prepn. given) was converted to the 2-hydroxy-1-oxoethyl deriv. which was treated with (F3CSO2)2O to give the 2-(trifluoromethylsulfonyloxy deriv. This compd. was stirred with HCONH2 and DMF to give I (R = R4 = Pr, R1 = R2 = Me, Y = O, Z = H, n = 1, p = 0) which was stirred with LiOH to give I (R = R4 = Pr, R1 = Me, R2 = Z = H, Y = O, n = 1, p = 0) (II). II and other title compds. showed LTB4 antagonism.

L10 ANSWER 25 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 137856-08-7 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[4-(3-isoxazolyl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C29 H35 N O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 116:6555 CA
TI Preparation of [(azolylphenoxy)alkoxy]benzopyrancarboxylates as antiinflammatories
IN Djuric, Stevan W.; Penning, Thomas D.
PA Searle, G. D., and Co., USA
SO U.S., 11 pp.

CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5051438	A	19910924	US 1990-524765	19900516
	CA 2083040	AA	19911117	CA 1991-2083040	19910503
	WO 9117989	A1	19911128	WO 1991-US3068	19910503
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	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	AU 9178925	A1	19911210	AU 1991-78925	19910503
	EP 528935	A1	19930303	EP 1991-909729	19910503
	EP 528935	B1	19941019		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05506440	T2	19930922	JP 1991-509234	19910503
	ES 2062792	T3	19941216	ES 1991-909729	19910503
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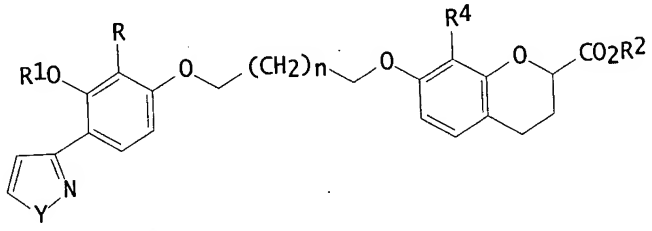

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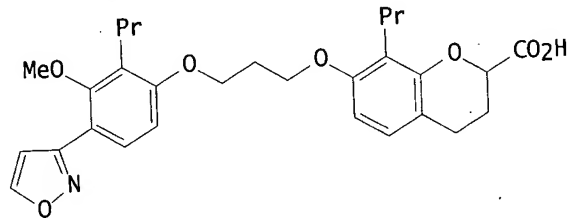
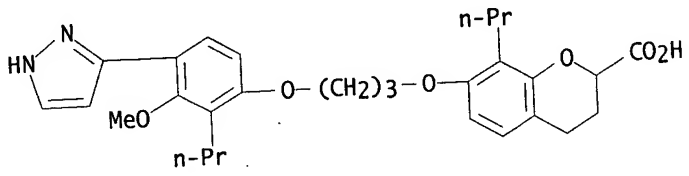


II

AB Title compds. (I; R = alkyl, alkenyl, alkynyl, cycloalkylalkyl; R1, R4 = alkyl; R2 = H, alkyl; Y = NH, O; n = 1-5), were prepd. Thus, Me 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate was O-methylated with MeI/K2CO3 in acetone. The product was condensed with Me2NCH(OMe)2 in DMF and the enaminone product was refluxed with H2NOH.HCl in MeOH/H2O to give, after sapon., title compd. II. II antagonized LTB4-induced chemotaxis of human neutrophils with 0.25 of the potency of 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid.

L10 ANSWER 26 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 137837-12-8 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-7-[3-[3-methoxy-2-propyl-4-(1H-pyrazol-3-yl)phenoxy]propoxy]-8-propyl- (9CI) (CA INDEX NAME)

FS 3D CONCORD
MF C29 H36 N2 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 122:230123 CA
TI Second Generation Leukotriene B4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore
AU Penning, Thomas D.; Djuric', Stevan W.; Miyashiro, Julie M.; Yu, Stella; Snyder, James P.; Spangler, Dale; Anglin, Charles P.; Fretland, Donald J.; Kachur, James F.; et al.
CS Department of Chemistry, Searle Research and Development, Skokie, IL, 60077, USA
SO Journal of Medicinal Chemistry (1995), 38(6), 858-68
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB The previous reports have highlighted the first-generation leukotriene B4 (LTB4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure-activity relation studies, in which a series of heterocyclic replacements for the Me ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was significantly more potent than SC-41930 in LTB4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, i.v., and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatog. and both demonstrated good in vitro and in vivo activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clin. candidate for psoriasis and ulcerative colitis therapy.

REFERENCE 2

AN 116:6555 CA
TI Preparation of [(azolylphenoxy)alkoxy]benzopyrancarboxylates as antiinflammatories
IN Djuric, Stevan W.; Penning, Thomas D.
PA Searle, G. D., and Co., USA

SO U.S., 11 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5051438	A	19910924	US 1990-524765	19900516
	CA 2083040	AA	19911117	CA 1991-2083040	19910503
	WO 9117989	A1	19911128	WO 1991-US3068	19910503
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU, US				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	AU 9178925	A1	19911210	AU 1991-78925	19910503
	EP 528935	A1	19930303	EP 1991-909729	19910503
	EP 528935	B1	19941019		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05506440	T2	19930922	JP 1991-509234	19910503
	ES 2062792	T3	19941216	ES 1991-909729	19910503
PRAI	US 1990-524765	19900516			
	WO 1991-US3068	19910503			

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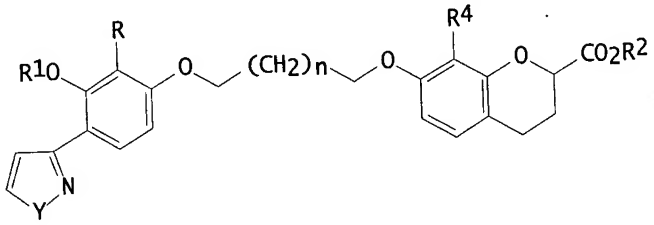

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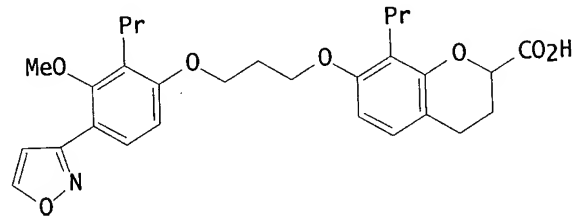


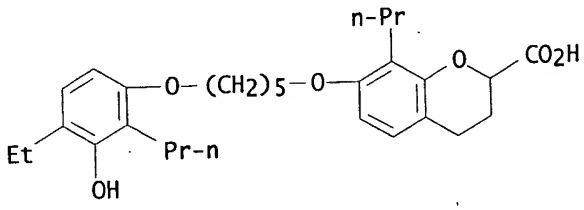
II

AB Title compds. (I; R = alkyl, alkenyl, alkynyl, cycloalkylalkyl; R1, R4 = alkyl; R2 = H, alkyl; Y = NH, O; n = 1-5), were prepd. Thus, Me 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate was O-methylated with MeI/K2CO3 in acetone. The product was condensed with Me2NCH(OMe)2 in DMF and the enaminone product was refluxed with H2NOH.HCl in MeOH/H2O to give, after sapon., title compd. II. II antagonized LTB4-induced chemotaxis of human neutrophils with 0.25 of the potency of 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid.

L10 ANSWER 27 OF 27 REGISTRY COPYRIGHT 2003 ACS
RN 99453-93-7 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 7-[[5-(4-ethyl-3-hydroxy-2-

propylphenoxy)pentyl]oxy]-3,4-dihydro-8-propyl- (9CI) (CA INDEX NAME)

FS 3D CONCORD
MF C29 H40 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

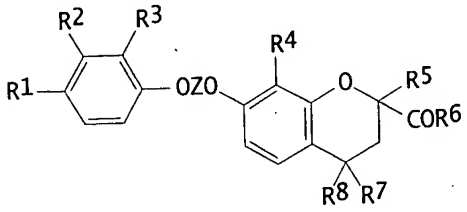
1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 104:5775 CA
TI Substituted dihydrobenzopyran-2-carboxylates
IN Miyano, Masateru; Shone, Robert Larry
PA Searle, G. D., and Co., USA
SO Eur. Pat. Appl., 48 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 150447	A2	19850807	EP 1984-115838	19841219
	EP 150447	A3	19860528		
	EP 150447	B1	19900124		
	R: DE, FR, GB, IT				
	US 4565882	A	19860121	US 1984-568846	19840106
	JP 60158187	A2	19850819	JP 1985-74	19850104
	JP 06031206	B4	19940427		
PRAI	US 1984-568846	19840106			

GI



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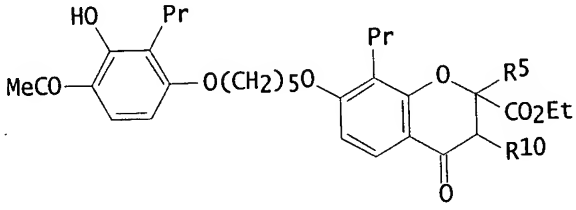

II

AB Antiallergy and antiinflammatory (no data) title compds. I (R1 = H, Et, MeCO, MeCHOH, EtO2C; R2 = H, OH, alkanoyloxy, CH2:CHCH2CH2CO2; R3, R4 = H, alkyl, CH2:CHCH2; R5 = H, alkanoyl; R6 = H, R9O; R7 = H, R8 = H, OH, alkoxy, CH2:CHCH2CH2O; R7R8 = O; R9 = H, alkyl, alkali metal, ammonium; Z = (hydroxy)alkylene] were prepd. Thus, 3,2,4-Pr(HO)2C6H2COMe was alkylated with Br(CH2)5Br to give 73% 2,3,4-Pr(HO)(MeCO)C6H2O(CH2)5Br. This was condensed with Et 7-hydroxy-8-propyl-4-oxo-4H-1-benzopyran-2-carboxylate to give 44% (pentyloxy)chromone II (R5R10 = bond) which was hydrogenated over Raney Ni to give 51% II (R5, R10 = H).